IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO.,	)	
Plaintiffs,	)	
	)	C. A. No. _____
v.	)	
IMPAX LABORATORIES, INC.,	)	
Defendant.	)	

COMPLAINT

Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest"), for their Complaint against defendant Impax Laboratories, Inc. ("Impax"), allege as follows.

1. In this action, Endo and Penwest seek to block Impax's abuse of the statutory and regulatory system that Congress has carefully constructed for resolving patent disputes when a drug company seeks approval to market a generic version of a branded drug product by filing an Abbreviated New Drug Application ("ANDA").

2. As Impax has publicly acknowledged, it does not even have an ANDA actually on file with respect to Endo's OPANA® ER pain relief product. The U.S. Food and Drug Administration ("FDA") rescinded its initial acceptance of Impax's ANDA.

3. Undaunted by this fact, however, and in direct defiance of FDA's decision to rescind acceptance of its ANDA and direct violation of applicable FDA regulations, Impax has forged ahead and tried to trigger the ANDA litigation process. The reason for Impax's improper conduct is clear—Impax wants to gain an unfair and unlawful advantage against Endo, Penwest, and Impax's generic competitors, in the hope that it can reap the

significant financial rewards potentially available to the first generic manufacturer to reach the market with a generic version of OPANA® ER.

4. The Court should put an immediate end to Impax's gamesmanship, and clear up any uncertainty regarding Endo and Penwest's intellectual property rights and their ability to enforce their patent portfolio relating to OPANA® ER, by declaring Impax's attempt to trigger the ANDA litigation process to be improper and without legal effect.

5. Moreover, it is clear that Impax's proposed generic product infringes Plaintiffs' patents, and in the alternative, Impax should be enjoined from selling any such generic product before the expiration of those patents.

PARTIES

6. Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty pharmaceutical company engaged in the research, development, sale and marketing of prescription pharmaceuticals used primarily to treat and manage pain, including OPANA® ER.

7. Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. Penwest is a drug development company focused primarily on the identification, development and commercialization of products for diseases of the nervous system using its expertise in drug development and drug delivery technology, including the extended-release technology used in OPANA® ER.

8. Upon information and belief, Impax is a Delaware corporation, having its principal place of business at 30831 Huntwood Avenue, Hayward, California 94544.

9. Upon information and belief, Impax is manufacturing generic drug products for sale and use throughout the United States, including in this judicial district.

NATURE OF ACTION

10. This is an action for declaratory judgment and, in the alternative, for infringement of United States Patent Nos. 5,662,933 ("the '933 patent") and 5,958,456 ("the '456 patent"). This action is based upon the Declaratory Judgment Act, 28 U.S.C. § 2201, *et seq.*, and the Patent Laws of the United States, 35 U.S.C. § 100, *et seq.*

JURISDICTION AND VENUE

11. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and 28 U.S.C. §§ 2201 and 2202. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

FACTUAL BACKGROUND

The Drug Approval Process

12. A company seeking to market a new pharmaceutical drug in the United States must first obtain approval from FDA, typically through the filing of a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(a). The sponsor of the NDA is required to submit information on all patents claiming the drug that is the subject of the NDA, or a method of using that drug, to FDA, and FDA then lists such patent information in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book." *See* 21 U.S.C. § 355(b)(1) and (c)(2).

13. On the other hand, a company seeking to market a generic version of a previously approved drug is not required to submit a full NDA. Instead, it may file an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355(j). The generic drug approval process is considered "abbreviated" because the generic manufacturer may piggyback

on the innovator company's data and FDA's prior finding of safety and efficacy by demonstrating, among other things, that the generic product is bioequivalent to the previously approved drug (the "listed drug" or "branded drug").

14. In conjunction with this "abbreviated" application process, Congress has put in place a process for resolving patent disputes relating to generic drugs, pursuant to which an ANDA filer must provide certifications addressing each of the patents listed in the Orange Book for the branded drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). An ANDA filer may certify, for instance, that it believes a patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4). This is known as a so-called "Paragraph IV Certification."

15. The filer of an ANDA with a Paragraph IV Certification must also provide notice to both the owner of the listed patent and the holder of the NDA for the referenced listed drug. This "Paragraph IV Notice" must include a detailed statement of the factual and legal bases for the applicant's belief that the challenged patent is invalid or not infringed by the proposed generic product. 21 U.S.C. § 355(j)(2)(B); 21 C.F.R. § 314.95.

16. If the patentee or NDA holder files a patent infringement action within 45 days of receiving a Paragraph IV Notice from an ANDA filer, final approval of the ANDA is generally subject to a 30-month stay. *See* 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3). The 30-month stay is important to innovator companies, such as Endo and Penwest, because it protects them from the severe financial harm that could otherwise ensue from FDA granting approval to a potentially infringing product without first providing an opportunity for the infringement case to be resolved. Put another way, the innovator company

is assured of a 30-month period during which it may try to enforce its intellectual property rights and resolve any patent dispute before the generic product enters the market. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

17. There are powerful incentives for generic companies to obtain the earliest possible filing date by jumping the gun with incomplete ANDA filings. The earliest ANDA filer may be entitled to 180 days of market exclusivity, during which time no other ANDA filer may come to market with a competing generic product. 21 U.S.C. § 355(j)(5)(B)(iv). By filing prematurely, the first ANDA filer may also be able to manipulate the rules surrounding the 30-month stay to its advantage.

18. The legislative history of the relevant statutory provisions reveals that Congress was clearly concerned about generic applicants filing incomplete or sham ANDAs to obtain an unfair and undeserved regulatory advantage at the expense of both innovator companies and other generic manufacturers.

19. Accordingly, one of the important protections built into the ANDA process is that a generic applicant may not even send a Paragraph IV Notice until it "receives from FDA an acknowledgment letter stating that its abbreviated new drug application is sufficiently complete to permit a substantive review." 21 C.F.R. § 314.95(b).

20. This safeguard makes simple common sense. Incomplete or sham ANDAs risk burdening the judicial system with premature, and perhaps entirely unnecessary, patent infringement litigation. If the incomplete or sham ANDA is never substantially completed, there would be no reason to force the parties and the courts through infringement litigation. Accordingly, the ANDA applicant may not trigger the litigation process by serving a

Paragraph IV Notice unless and until it has an ANDA on file that FDA has accepted for substantive review.

Endo's NDA on OPANA® ER

21. On June 22, 2006, FDA approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which contain oxymorphone hydrochloride, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

22. Previously, on September 2, 1997, the U.S. Patent and Trademark Office ("PTO") duly and legally issued the '933 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. Edward Mendell Co., Inc. was renamed Penwest Pharmaceuticals Co. on October 20, 1997. A true and correct copy of the '933 patent is attached as Exhibit A.

23. Also, on September 28, 1999, the PTO duly and legally issued the '456 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co., Inc., as assignee. A true and correct copy of the '456 patent is attached as Exhibit B.

24. On October 2, 2007, the PTO duly and legally issued United States Patent No. 7,276,250 ("the '250 patent"), entitled "Sustained Release Formulations Of Oxymorphone," to Penwest, as assignee. A true and correct copy of the '250 patent is attached as Exhibit C.

25. On that same day, Endo submitted information regarding the '250 patent to FDA for listing in the Orange Book with respect to OPANA® ER tablets. FDA thereafter listed the '250 patent in the Orange Book with respect to OPANA® ER tablets, pursuant to 21 C.F.R. § 314.53(e).

26. On October 19, 2007, Endo submitted information regarding the '933 and '456 patents to FDA for listing in the Orange Book with respect to OPANA® ER tablets. FDA thereafter listed the '933 and '456 patents in the Orange Book with respect to OPANA® ER tablets, pursuant to 21 C.F.R. § 314.53(e).

27. Penwest is the assignee and owner of the '250, '933 and '456 patents, and Endo is an exclusive licensee of these patents in the relevant field of use pursuant to a strategic alliance agreement with Penwest.

Impax's Incomplete ANDA

28. Upon information and belief, on or prior to October 2, 2007, Impax submitted to FDA paperwork purporting to constitute an ANDA under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of oxymorphone hydrochloride extended-release tablets, as generic versions of OPANA® ER tablets.

29. On October 2, 2007, Impax sent Penwest and Endo a notice ("Impax Notice 1") stating that that it had submitted ANDA No. 79-087 seeking approval to manufacture, use, or sell generic oxymorphone hydrochloride extended-release tablets prior to the expiration of the '250 patent.

30. On October 3, 2007, Penwest and Endo each received Impax Notice 1, which purported to "provide the notice and information required by 21 U.S.C. § 355(j)(2)(B)(i) and (ii) (§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax . . . has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data . . . ."

31. Impax Notice 1 also advised Penwest and Endo that Impax's ANDA included a Paragraph IV Certification that, in Impax's opinion, the proposed manufacture, importation, use or sale of the generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '250 patent. Impax did not assert that the '250 patent was either invalid or unenforceable.

The Impax Press Release

32. On October 4, 2007, Impax issued a press release ("Impax Press Release") stating it had submitted an ANDA to FDA and had sent Penwest and Endo a Paragraph IV Notice.

33. In the Impax Press Release, Impax stated that its Paragraph IV Notice asserted that the proposed generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '250 patent, *and* that those claims are invalid and/or unenforceable. A true and correct copy of the Impax Press Release is attached as Exhibit D.

34. The Impax Press Release was false, as Impax Notice 1 does not assert that the '250 patent is invalid or unenforceable.

35. Furthermore, notwithstanding the fact that it had served a purported Paragraph IV Notice on Endo and Penwest, Impax admitted in the Impax Press Release that FDA *"has rescinded its initial acceptance"* of its ANDA and that its was *"working with the FDA to correct any deficiencies of the ANDA."*

36. Thus, no later than October 4, 2007, and upon information and belief before that date, Impax was well aware that it did not have a valid and subsisting ANDA that

FDA had accepted for substantive review, and it was well aware that it had no right to trigger the ANDA litigation process by sending Endo and Penwest any Paragraph IV Notices.

Impax's Invalid Post-Press Release Notices

37. After notifying the world through its press release that the acceptance of its ANDA had been rescinded, Impax inundated Endo and Penwest with five additional Paragraph IV Notices, all in violation of the FDA regulations.

38. For instance, on each of October 3, 4, 5 and 9, Impax sent to Endo and Penwest an additional Paragraph IV Notice with respect to the '250 patent, each of which was substantively identical to Impax Notice 1 ("Impax Notices 2-5"). In each of those Notices, Impax falsely stated that it was sending the Notices pursuant to an ANDA, when in fact, Impax knew it did not have a valid ANDA on file and was prohibited by law from sending Paragraph IV Notices.

39. Thus, Impax purported to serve each of Impax Notices 1-5 pursuant to a valid ANDA at a time when Impax knew it had no valid ANDA on file and accepted by FDA for substantive review.

40. Impax had no right to trigger the ANDA litigation process with respect to the '250 patent because FDA had rescinded acceptance of Impax's ANDA.

41. By letter dated October 29, 2007, Impax sent Penwest and Endo a purported Paragraph IV Notice with respect to the '933 and '456 patents (Impax Notice 6).

42. Impax Notice 6 again purported to "provide the notice and information required by 21 U.S.C. § 355(j)(2)(B)(i) and (ii) (§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax . . . has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data . . . ."

43. Impax Notice 6 advised Penwest and Endo that Impax's ANDA included Paragraph IV Certifications asserting that, in Impax's opinion, the manufacture, use, sale or offer for sale of the proposed generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '933 or '456 patents. Impax Notice 6 does not assert that either patent is invalid or unenforceable.

44. Like the invalid Notices on the '250 patent, Impax purported to serve Impax Notice 6 pursuant to a valid ANDA at a time when Impax knew that it had no valid ANDA on file and accepted by FDA for substantive review.

45. As with the '250 patent, Impax had no right to trigger the ANDA litigation process with respect to the '933 or '456 patents because FDA had rescinded acceptance of Impax's ANDA

46. Penwest and Endo demanded that Impax withdraw Impax Notices 1-6, but Impax has refused, and continues to refuse, to retract these unlawful Notices. Impax has also refused to provide Endo or Penwest with even the most basic information regarding FDA's rescission of its ANDA, including the date on which Impax first learned that FDA rescinded its initial acceptance or the basis for FDA's rescission.

COUNT I

DECLARATORY JUDGMENT

47. Plaintiff incorporates each of the preceding paragraphs 1 to 46 as if fully set forth herein.

48. It is undisputed that, at least as early as October 4, 2007, and upon information and belief earlier, FDA had rescinded its acceptance of Impax's ANDA.

49. Upon information and belief, Impax still does not have any ANDA for generic oxymorphone hydrochloride extended-release tablets accepted by and pending before FDA.

50. Absent an ANDA that has been accepted by FDA for substantive review, Impax has no legitimate basis to trigger the ANDA patent infringement litigation process. As a consequence, all of the Paragraph IV Notices Impax sent to Endo and Penwest, beginning with Impax Notice 1 dated October 2, 2007, were improper, null, void, and without legal effect.

51. Endo and Penwest have asked Impax to withdraw its improperly served Paragraph IV Notices, but Impax has refused to do so.

52. An actual and substantial justiciable controversy exists between Endo and Penwest, on the one hand, and Impax, on the other, as to whether Impax's Paragraph IV Notices are null, void and without legal effect, and as a consequence, whether Impax properly triggered the ANDA litigation process by serving Impax Notices 1-6 on Endo and Penwest.

53. Impax's improper service of Impax Notices 1-6, and its subsequent refusal to withdraw those Notices, has resulted in what might be entirely unnecessary patent infringement litigation. At the very least, any patent infringement litigation as part of the ANDA litigation process is premature until Impax has an ANDA that has been accepted by FDA for substantive review.

54. In addition, Impax's refusal to withdraw its improper Paragraph IV Notices has created an actual controversy and cloud of uncertainty surrounding the rights of Endo, Penwest and others under the statutory and regulatory scheme carefully constructed by Congress. That controversy includes, without limitation, whether Endo and Penwest are obligated to file suit for infringement under 35 U.S.C. § 271(e) within 45 days of receiving

Impax Notices 1-6 in order to preserve their statutory rights to a thirty-month stay of approval of Impax's ANDA as provided by 21 U.S.C. § 355(j)(5)(B)(iii), and whether Impax has co-opted for itself, to the detriment of other generic manufacturers, the 180-day market exclusivity afforded by 21 U.S.C. § 355(j)(5)(B)(iv).

55. The controversy as to the validity and effectiveness of Impax's Paragraph IV Notices will cause Endo and Penwest, as well as Impax's generic competitors, to suffer substantial prejudice unless the controversy and corresponding cloud of uncertainty is resolved by the Court.

56. Accordingly, Endo and Penwest are entitled to a declaration that: (1) Impax's Paragraph IV Notices are null, void and without legal effect and that Impax was not entitled to trigger the ANDA patent litigation process with the respect to the '250, '933 and '456 patents; (2) this Court has no subject matter jurisdiction over claims between Plaintiffs and Impax regarding infringement of the '250, '933 and '456 patents because the Paragraph IV Notices served by Impax are null, void and of no legal effect; (3) the Paragraph IV Notices served by Impax did not commence the 45-day period for filing a patent infringement action pursuant to 21 U.S.C. § 355(j)(5)(B)(iii); and (4) if and when FDA accepts Impax's ANDA, Impax must submit and serve on Endo and Penwest new patent notices at that time pursuant to 21 U.S.C. § 355(j)(2)(A)(vii).

COUNT II

INFRINGEMENT OF THE '456 PATENT

57. Plaintiff incorporates each of the preceding paragraphs 1 to 56 as if fully set forth herein.

58. For the reasons explained above, Impax has no ANDA that has been accepted for review by FDA, and accordingly, its Paragraph IV Notices are null, void and of no effect. Alternatively, however, in the event that Impax's Paragraph IV Notices are deemed to be effective, the submission of its ANDA to FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '456 patent under 35 U.S.C. § 271(e)(2)(A).

59. Impax's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '456 patent.

60. Upon information and belief, Impax was aware of the existence of the '456 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the filing of its Paragraph IV Certification with respect to the '456 patent constitutes infringement of that patent.

61. Impax served Endo and Penwest with the Paragraph IV Notice concerning the '456 patent in bad faith, with knowledge that it was improper, null, void, and without legal effect.

COUNT III

INFRINGEMENT OF THE '933 PATENT

62. Plaintiff incorporates each of the preceding paragraphs 1 to 61 as if fully set forth herein.

63. For the reasons explained above, Impax has no ANDA that has been accepted for review by FDA, and accordingly, its Paragraph IV Notices are null, void and of no effect. Alternatively, however, in the event that Impax's Paragraph IV Notices are deemed to be effective, the submission of its ANDA to FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '933 patent under 35 U.S.C. § 271(e)(2)(A).

64. Impax's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '933 patent.

65. Upon information and belief, Impax was aware of the existence of the '933 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the filing of its Paragraph IV Certification with respect to the '933 patent constitutes infringement of that patent.

66. Impax served Endo and Penwest with the Paragraph IV Notice concerning the '933 patent in bad faith, with knowledge that it was improper, null, void, and without legal effect.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A declaration that Impax's Paragraph Notices are null, void and without legal effect and that Impax was not entitled to trigger the ANDA patent litigation process with the respect to the '250, '933 and '456 patents;

B. A declaration that this Court has no subject matter jurisdiction over claims between Plaintiffs and Impax regarding infringement of the '250, '933 or '456 patents because the Paragraph IV Notices served by Impax are null, void and without legal effect;

C. A declaration that the Paragraph IV Notices served by Impax did not commence the 45-day period for filing a patent infringement action pursuant to 21 U.S.C. § 355(j)(5)(B)(iii);

D. A declaration that if and when FDA accepts Impax's ANDA for substantive review, Impax must submit and serve on Endo and Penwest at that time new Paragraph IV Certifications and Notices pursuant to 21 U.S.C. § 355(j)(2)(A)(vii);

E. In the alternative, in the event the Court determines that Impax's Paragraph IV Notices are not null and void, Endo and Penwest seek the following additional relief:

(1) A judgment that Impax has infringed the '456 patent;

(2) A judgment that Impax has infringed the '933 patent;

(3) An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of Impax's ANDA No.79-087 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), shall not be earlier than the expiration date of the '456 and '933 patents, including any extensions;

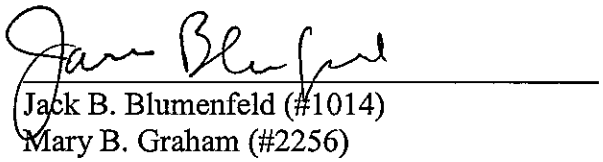
(4) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Impax, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringement of the '456 and '933 patents for the full terms thereof, including any extensions; and

(5) A declaration that this is an exceptional case and an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP



Jack B. Blumenfeld (#1014)
Mary B. Graham (#2256)
Julia Heaney (#3052)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

Of Counsel:

Martin J. Black
George G. Gordon
Ann M. Caviani Pease
Robert D. Rhoad
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
(215) 994-4000
Attorneys for Plaintiff Endo Pharmaceuticals Inc.

Robert J. Gunther, Jr.
Lisa J. Pirozzolo
James P. Barabas
WILMER CUTLER PICKERING HALE AND DORR LLP
399 Park Avenue
New York, New York 10022
(212) 230-8800
Attorneys for Plaintiff Penwest Pharmaceuticals Co.

November 15, 2007

EXHIBIT A

US005662933A

United States Patent [19]

Baichwal et al.

[11] Patent Number: 5,662,933

[45] Date of Patent: *Sep. 2, 1997

[54] **CONTROLLED RELEASE FORMULATION (ALBUTEROL)**

[75] Inventors: **Anand Baichwal**, Wappingers Falls, N.Y.; **Troy W. McCall**, New Milford, Conn.

[73] Assignee: **Edward Mendell Co., Inc.**, Patterson, N.Y.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,455,046.

[21] Appl. No.: **553,008**

[22] Filed: **Nov. 3, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 118,924, Sep. 9, 1993, Pat. No. 5,455,046.

[51] **Int. Cl.**[6] **A61K 9/14**; A61K 9/22

[52] **U.S. Cl.** **424/457**; 424/468; 424/488; 514/777; 514/778; 514/779; 514/780; 514/781; 514/964; 514/965

[58] **Field of Search** 424/457, 468, 424/488; 514/777, 778, 779, 780, 781, 964, 965

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Primary Examiner—Nathan M. Nutter
Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] **ABSTRACT**

A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.

48 Claims, 3 Drawing Sheets

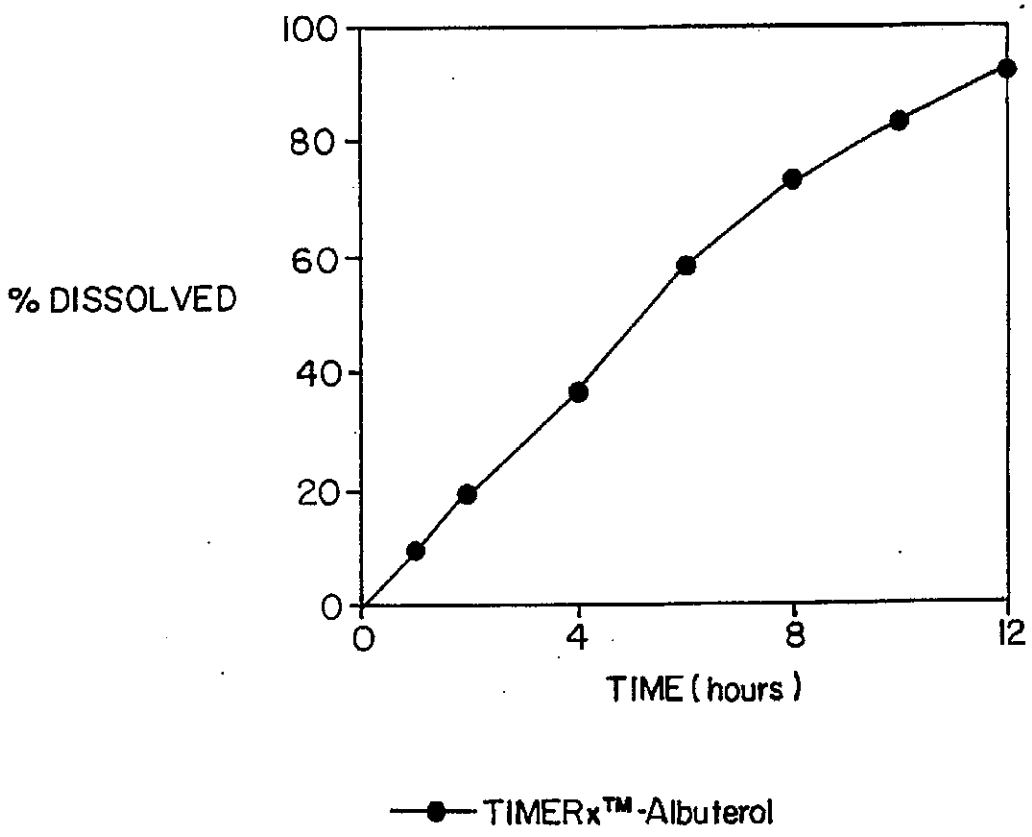
100
80
60
40
20
0
% DISSOLVED
0
4
8
12
TIME (hours)
TIMERx™-Albuterol

FIG. 1

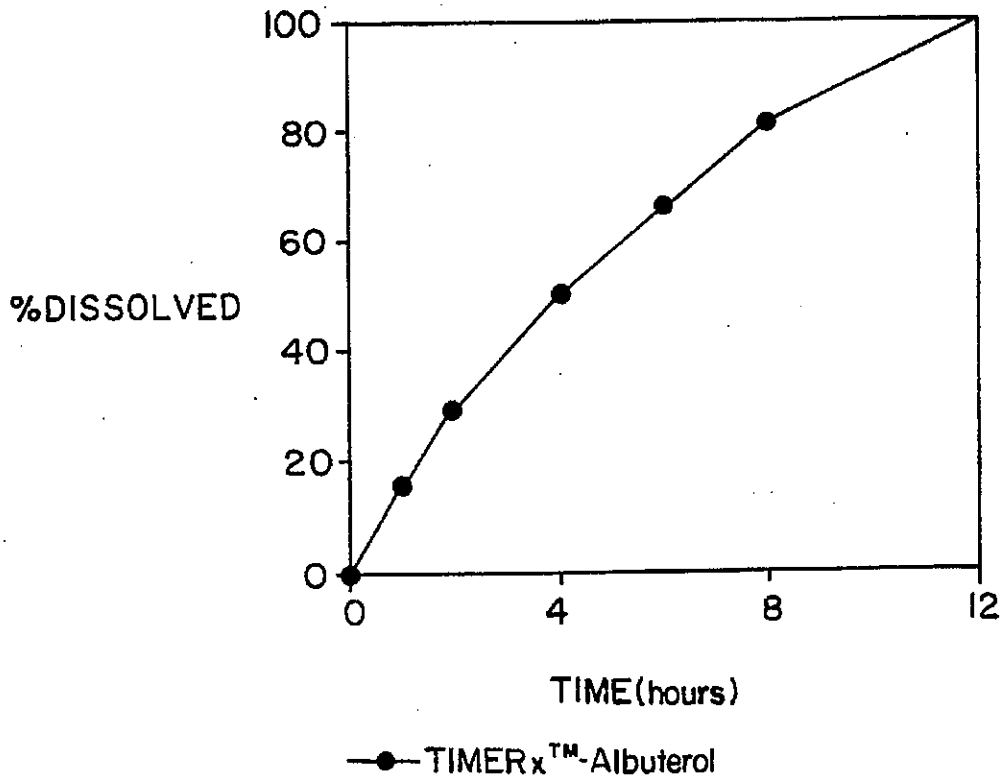
100
80
60
40
20
0
%DISSOLVED
0
4
8
12
TIME(hours)
TIMERx™-Albuterol

FIG. 2

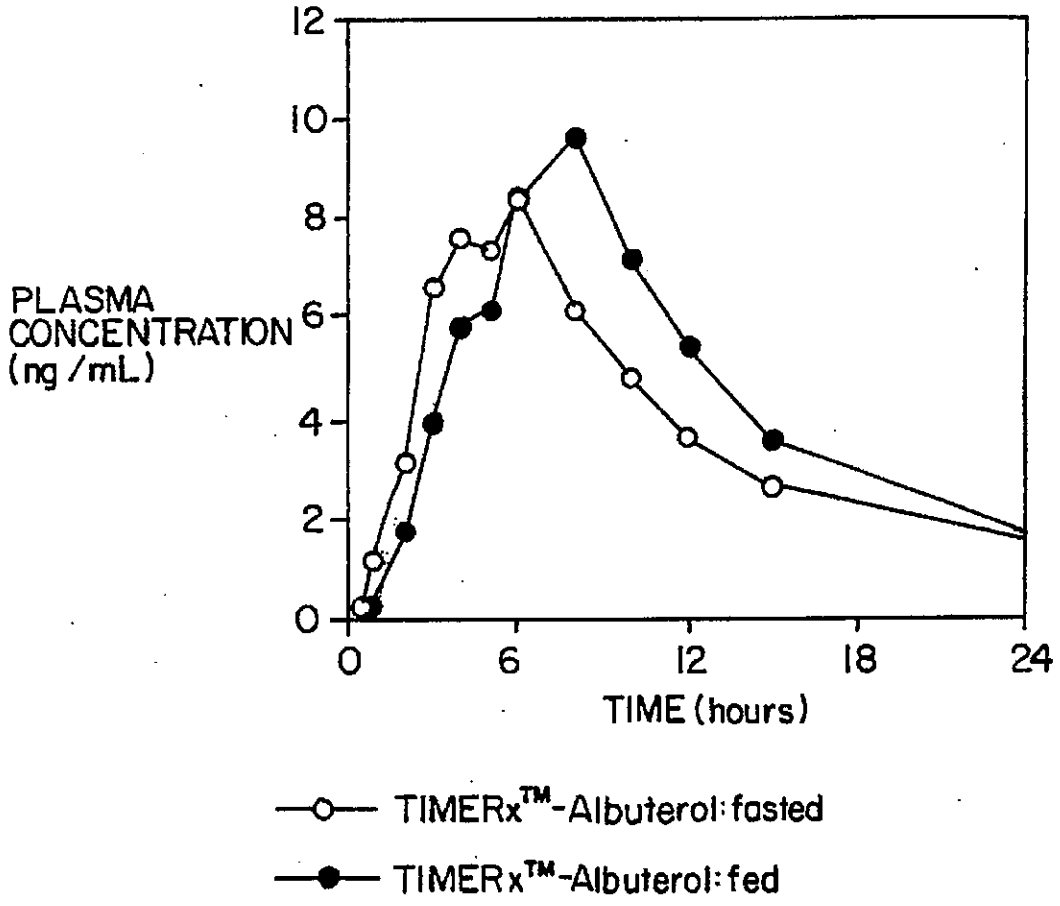
PLASMA CONCENTRATION (ng/mL)
12
10
8
6
4
2
0
0
6
12
18
24
TIME (hours)
TIMERx™-Albuterol: fasted
TIMERx™-Albuterol: fed

FIG. 3

CONTROLLED RELEASE FORMULATION (ALBUTEROL)

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. application Ser. No. 08/118,924, filed on Sep. 9, 1993, and now U.S. Pat. No. 5,455,046 the disclosure of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to controlled release formulations which may be blended with a wide range of therapeutically active medicaments and made into controlled release solid dosage forms for oral administration.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number administrations. These advantages have been attained by a wide variety of methods. For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. In U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, hereby incorporated by reference in their entireties, it is reported that a controlled release excipient which is comprised of a synergistic combination of heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum, in an aqueous environment) is capable of being processed into oral solid dosage forms using either direct compression (i.e., dry granulation), following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the trade name TIMERx® from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-release pharmaceutical formulation containing xanthan gum wherein the xanthan gum comprises from about 7.5 to about 28 percent, by weight, of the formulation except for a formulation wherein the controlled release carrier comprises a mixture of 15–50 parts by weight dimethylsiloxane, 30–100 parts by weight silicic acid, 30–100 parts by weight mannans or galactans or a mixture thereof, 50–150 parts by weight xanthans and 5–75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of a controlled release formulation providing a novel and unexpected combination of suitable proportions of a homopolysaccharide such as, e.g., xanthan gum, a heteropolysaccharide, such as, e.g., locust bean gum, together with an inert diluent and a pharmacologically acceptable hydrophobic material, so as to provide an improvement in controlled release properties for such an active medicament.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release formulation for a therapeutically active medicament.

It is a further object of the present invention to provide a method for preparing a controlled release formulation for a therapeutically active medicament.

It is yet another object of the present invention to provide a controlled release excipient which may be used in the preparation of a sustained release oral solid dosage form of a therapeutically active medicament that provides an even rate of release of an active medicament.

It is a further object of the present invention to provide a controlled release excipient which, when combined with an effective amount of a bronchodilator, such as albuterol, is suitable for providing a sustained release of that medicament so as to provide a therapeutically effective blood level of the medicament for e.g., 12 or 24 hours, without allowing an excessive early release of medication, and where the release kinetics are unaffected by the contents of the patient's gastrointestinal tract.

It is yet a further object of the present invention to provide a method for treating patients with an active medication in controlled release form.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in-part to a controlled release formulation comprising a therapeutically effective amount of a medicament, and a controlled release excipient comprising a gelling agent and a swelling agent, such as, for example, a homopolysaccharide, a heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention, the ratio of the heteropolysaccharide gum to the homopolysaccharide gum is from about 1:3 to about 3:1. More preferably, the ratio is about 1:1. Preferably, the heteropolysaccharide gum includes xanthan gum and the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a sustained release oral solid dosage form for albuterol or salts or derivatives thereof in an amount necessary to render a therapeutic effect in a human patient. The albuterol is present in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical diluent so that the ratio of the inert diluent to the gelling agent is from about 1:8 to about 8:1. Preferably, the diluent is from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing. The diluent can also be a saccharide such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

The dosage form optionally includes a pharmaceutically acceptable hydrophobic material. Any pharmaceutically acceptable hydrophobic material may be suitably employed.

Suitable hydrophobic materials include carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing. Preferably, the hydrophobic material selected from cellulose ether, a cellulose ester and an alkylcellulose, such as ethylcellulose and carboxymethylcellulose. The hydrophobic material may be included in the dosage form in an amount effective to slow the hydration of the gelling agent when exposed to an environmental fluid.

The hydrophobic material is preferably present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form, and can also be present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

The medicament can be any medicament for which an orally administered controlled release form is desired. Preferably, the formulation is prepared to include a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

The controlled release solid dosage form can be prepared in any conventional orally administered dosage form, including a tablet, as a granular form and as a granular form administered in a gelatin capsule containing a sufficient amount of the granules to provide an effective dose of the included therapeutically active medicament. For a tablet dosage form, at least part of a surface of the tablet can optionally be coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight. Further, a granular dosage form can optionally be coated with a hydrophobic coating material to a weight gain that ranges from about 1% to about 20%. The hydrophobic material can be selected from, e.g., a cellulose ether, a cellulose ester and an alkylcellulose. The hydrophobic material can optionally be applied before, during or after the process of tableting. In addition, if there is a need for an early release of the active medicament, the coating can optionally be formulated to include from about 10 to about 40 percent of the total amount of the active medicament in a quick release external layer.

The invention also relates to methods for preparing a controlled release solid dosage form as described above for providing an active medicament in an amount effective for treating a patient for from 12 to about 24 hours. The method includes the steps of preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and optionally from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament to provide a final product having a ratio of medicament to gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC_∞"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC_∞ ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

In addition, for example, mean peak plasma concentrations (Cmax) ranging from about 7 to about 12 ng/ml or even from about, 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a Cmax ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

In another example, time to mean peak plasma concentration (Tmax) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a Tmax ranging from about 3 to about 6 hours (fasting patient) or from about 3 to about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC_∞ (fasting patient) to AUC_∞ (fed patient) that range from about 0.50 to about 0.70.

Further still, the formulation provides, for example ranges of Cmax (fasting patient) divided by Cmax (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a gelling agent of both hetero- and homo-polysaccharides which exhibit synergism, e.g., the combination of two or more polysaccharide gums produce a higher viscosity and faster hydration than that which would be expected by either of the gums alone, the resultant gel being faster-forming and more rigid.

In the present invention, it has been found that a sustained release excipient comprising only the gelling agent (heterodisperse polysaccharides, e.g., xanthan gum and locust bean gum, may not be sufficient to provide a suitable sustained release of an active medicament to provide a 12 or 24 hour formulation, when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid.

In certain embodiments, the present invention is related to the surprising discovery that by granulating the sustained release excipient with a solution or dispersion of a pharmacologically acceptable hydrophobic material prior to admixture of the sustained release excipient with the medicament and tableting, the medicament may provide therapeutically effective blood levels for extended periods of time, e.g., from about 12 to about 24 hours. The hydrophobic material is present in a range from about 0 to about 90%, by weight, of the sustained release excipient and in a preferred embodiment, is present in a range from about 1 to 20 percent of the sustained release excipient or from about 25 to about 75 percent of the sustained release excipient.

The sustained release excipient can be granulated with a pharmacologically acceptable hydrophobic material such as, for, example, an alkylcellulose, a cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate "PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropylcellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, a pre-manufactured direct compression diluent, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used. If the mixture is to be manufactured without a wet granulation step, and the final product is to be tableted, it is preferred that all or part of the inert

diluent comprise a pre-manufactured direct compression diluent. Such direct compression diluents are widely used in the pharmaceutical arts, and may be obtained from a wide variety of commercial sources. Examples of such pre-manufactured direct compression excipients include Emcocel® (microcrystalline cellulose, N.F.), Emdex® (dextrates, N.F.), and Tab-Fine® (a number of direct-compression sugars including sucrose, fructose, and dextrose), all of which are commercially available from Edward Mendell Co., Inc., Patterson, N.Y.). Other direct compression diluents include Anhydrous lactose (Lactose N.F., anhydrous direct tableting) from Sheffield Chemical, Union, N.J. 07083; Elcems® G-250 (Powdered cellulose, N.F.) from Degussa, D-600 Frankfurt (Main) Germany; Maltrin® (Agglomerated maltodextrin) from Grain Processing Corp., Muscatine, IA 52761; Neosorb 60® (Sorbitol, N.F., direct-compression) from Roquette Corp., 645 5th Ave., New York, N.Y. 10022; Nu-Tab® (Compressible sugar, N.F.) from Ingredient Technology, Inc., Pennsauken, N.J. 08110; Polyplasdone XL® (Crospovidone, N.F., cross-linked polyvinylpyrrolidone) from GAF Corp., New York, N.Y. 10020; Primojel® (Sodium starch glycolate, N.F., carboxymethyl starch) from Generichem Corp., Little Falls, N.J. 07424; Solka Floc® (Cellulose floc) from Edward Mendell Co., Carmel, N.Y. 10512; Fast-Flo Lactose® (Lactose N.F., spray dried) from Foremost Whey Products, Baraboo, Wis. 53913 and DMV Corp., Vehgel, Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized starch, N.F., compressible) from Colorcon, Inc., West Point, Pa. 19486. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75 percent gelling agent, and from about 30 to about 75 percent inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75 percent gelling agent and from about 15 to about 65 percent inert diluent.

The sustained release excipient of the present invention may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic material may be selected from an alkylcellulose such as ethylcellulose such as carboxymethyl-cellulose ("CMC"), other hydrophobic cellulosic materials, acrylic and/or methacrylic ester polymers, copolymers of acrylic and methacrylic esters, zein, waxes, other hydrophobic cellulosic materials, cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP"), hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid.

In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20 percent by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC), Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g. 1:20 or 1:40) of quaternary ammonium compounds).

Once the sustained release excipient of the present invention has been prepared, it is then possible to blend the same with the medicament, e.g., in a high shear mixer. In one embodiment, the formulation is prepared by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, optionally followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include drugs ranging in solubility from water soluble to water insoluble. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), antitussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In a preferred embodiment, the therapeutically active agents are sympathomimetics such as, dobutamine hydrochloride, dopamine hydrochloride, ephedrine sulfate, epinephrine, fenfluramine hydrochloride, isoetharine, isoproterenol, mephentermine sulfate, metaproterenol sulfate, metaraminol bitartrate, methoxamine hydrochloride, norepinephrine bitartrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, ritodrine hydrochloride, terbutaline sulfate, tetrahydrozoline hydrochloride, triprolidine and pseudoephedrine, xylometazoline hydrochloride, isoproterenol and dobutamine as well as beta2 selective adrenergic agonists, including, for example, terbutaline, albuterol, isoetharine, pirbuterol and bitolterol (GOODMAN AND GILMAN'S, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Eighth Edition, the disclosure of which is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274

by the National Academy of Sciences, pages 63–258, incorporated herein in its entirety, may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857–884, hereby incorporated by reference in its entirety), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the inventive formulation can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following addition of drug and lubricant powder, or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In dry granulation techniques, the excipients, i.e., the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed with an active medicament and the mixture is then formed into tablets and the like by compression, without the addition of water or other solvent.

In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The sustained release excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. When the final product to be manufactured is tablets, the complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000–1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active (drug) is high, a pharmaceutical formulator may choose to wet granulate the active medicament with other excipients to attain a more compact tablet. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 300 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg.

The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an

average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic material, such as, e.g., a hydrophobic polymer, to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic material included in the tablet coating may be the same or different material as compared to the hydrophobic material which is optionally granulated with the sustained release excipient.

In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead or the hydrophobic coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100–555.

In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60°–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10μ if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2—selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

Preparation

The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or

capsules. Whatever the formulation, it is preferred that such pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

Dissolution Testing

The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

Bioavailability Study

A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC0-t, AUC0-∞, mean peak plasma concentration ("Cmax") and time to mean peak plasma concentration ("Tmax") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

EXAMPLES 1–2

Preparation of Controlled Release Formulations with Carboxymethylcellulose and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1–2 are set forth in Table 1 below:

TABLE 1

The hydrophobic polymer is carboxymethylcellulose ("CMC").

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt(mg)	334.6	204.7
Diameter (in)	3/8	3/8
Hardness (Kp)	6.5	2.6

The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

EXAMPLES 3–4

Preparation of Controlled Release Formulations with Cellulose Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra.

but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

Component	Example 3	Example 4
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15%
3. CAP	10	30
4. Dextrose	60	40
5. Water	10*	17*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

TABLE 5

Component	Example 3	Examples 4
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

TABLE 6

Time (hrs)	Example 3	Example 4
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.8	5.8

The tablet tested in Example 4 provided the most prolonged release in the dissolution test.

EXAMPLES 5–6

Preparation of Controlled Release Formulations with Polyvinyl Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

TABLE 7

Component	Example 5	Example 6
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. PVAP	10	30
4. Dextrose	60	40
5. Water	18*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

TABLE 8

Component	Example 5	Example 6
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

TABLE 9

Time (hrs)	Example 5	Example 6
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.9	8.6

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

EXAMPLES 7–8

Preparation of Controlled Release Formulations with Hydroxypropylmethylcellulose Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra,

but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

TABLE 10

Component	Example 7	Example 8
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. HPMCP	10	30
4. Dextrose	60	40
5. Water	13*	18*

*Removed during processing.

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

TABLE 11

Component	Example 7	Example 8
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

TABLE 12

Time (hrs)	Example 7	Example 8
0 (% release)	0.0	0.0
1	33.7	32.7
2	48.2	42.8
4	63.9	60.3
6	74.8	71.2
8	79.6	74.6
10	85.6	82.3
12	87.0	87.2
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

EXAMPLES 9–12

Preparation of Controlled Release Formulations with Ethylcellulose Coating and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1–2, supra, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9–12 are detailed by Table 13, below.

TABLE 13

Component	Excipient for Examples 9–12
1. Xanthan gum	12%
2. Locust bean gum	18
3. Dextrose	65
4. EAD*	5*

*EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease ® , from Colorcon.

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) was mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets were coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°–50° C.; charge per batch 1 kg; dry air—Conair Prostyle 1250. 60°–70° C.). The tablets were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The proportions of the tablets are set forth in Table 14 below:

TABLE 14

Component	Percent
1. SRE*	8.2%
2. Albuterol sulfate	5.3
3. Polyvinyl acetate phthalate	5.0
4. Sodium stearyl fumarate	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 15, below. The columns are identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex. 11) and 4% (Ex. 12) coating by weight.

TABLE 15

Time (hrs)	Ex. 9 Uncoated	Ex. 10 2%	Ex. 11 3%	Ex. 12 4% (coat % w/w)
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5
Tablet wt (mg)	181.4			
Diameter (in)	3/8			
Hardness (Kp)	7.9			

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9–12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH—time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16

Fed/Fast Dissolution Protocol

	"Fasted"		"Fed"
Apparatus:	Type III		Type III
Media:	0–1 hr	pH 1.5	30% peanut oil
	1–2 hr	pH 3.5	
	2–4 hr	pH 5.5	
	4–12 hr	pH 7.5	
Agitation:	15 cpm		15 cpm
Volume:	250 mL		250 mL

TABLE 17

Fed/Fast Dissolution Results

Time (hrs)	"Fasted" Uncoated	"Fasted" 2%	"Fed" Uncoated	"Fed" 2%
0 (% release)	0.0	0.0	0.0	0.0
1	48.8	15.5	28.8	18.4
2	68.5	28.8	49.8	39.9
4	87.2	49.5	91.9	78.9
6	96.1	65.9	100.0	97.3
8	100.0	80.7	100.0	100.0
12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

RESULTS AND DISCUSSION

FIGS. 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in FIG. 3. FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of FIG. 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 through 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max}, T_{max}, and AUC_{∞} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

TABLE 18

Albuterol Pharmacokinetics

Parameter		TIMERx fasted	TIMERx fed
Cmax	mean	10.5	10.6
	%CV	39.0	31.0
Tmax	mean	4.5	7.0
	%CV	29.0	23.0
AUCInf	mean	113.4	128.1
	%CV	30.0	20.0

Ratios	Cmax	Tmax	AUC Inf
TIMERx fasted: TIMERx fed	0.98	0.64	0.89
TIMERx fed: TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

TABLE 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC_{∞}	57.3–156.2	75.6–161.1
Cmax	4.6–18.4	6.0–15.9
Tmax	3.0–6.0	3.0–8.0

Parameter	TIMERx-fed
AUC_{∞}	89.9–149.2
Cmax	7.0–11.9
Tmax	3.0–10.0

CONCLUSION

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

a sustained release excipient comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of reciprocally cross-linking when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid and

a pharmaceutically acceptable hydrophobic material.

2. The controlled release solid dosage form according to claim 1 wherein said diluent is a saccharide selected from the group consisting of sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

3. The controlled release solid dosage form according claim 1, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

4. The controlled release solid dosage form according claim 2, wherein said xanthan gum and said locust bean gum are present in about a 1:1 ratio, respectively, by weight.

5. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

6. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

7. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form.

8. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

9. The controlled release solid dosage form according to claim 1 wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

10. The controlled release solid dosage form according to claim 1 which is a tablet.

11. The controlled release solid dosage form according to claim 1 which is in granular form.

12. The controlled release solid dosage form according to claim 11, which comprises a gelatin capsule containing a sufficient amount of said granules to provide an effective dose of said therapeutically active medicament.

13. The controlled release solid dosage form according to claim 9, wherein said hydrophobic material is selected from the group consisting of carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, and mixtures of any of the foregoing, prior to incorporation of said medicament, said hydrophobic material being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

14. The controlled release solid dosage form according to claim 12 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

15. The controlled release solid dosage form according to claim 1 which comprises a granulation which is coated with a hydrophobic material to a weight gain from about 1% to about 20%.

16. The controlled release solid dosage form according to claim 14, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

17. The controlled release solid dosage form according to claim 16 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

18. The controlled release solid dosage form according to claim 17, wherein said mixture of sustained release excipient and medicament are coated with a hydrophobic material prior to tableting.

19. The controlled release solid dosage form according to claim 1 which is a tablet, said tablet further comprising a coating containing from about 10 to about 40 percent of the total amount of said medicament included in said dosage form.

20. The controlled release solid dosage form according to claim 1 wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

21. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of a medicament thereto, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

22. The method of claim 21, further comprising tableting said mixture of said sustained release excipient and said medicament.

23. The method of claim 21, further comprising coating said tablets with a hydrophobic coating to a weight gain from about 1% to about 20%.

24. The method of claim 21, further comprising granulating said sustained release excipient with a hydrophobic material.

25. The method of claim 21, wherein said medicament is albuterol or a salt or derivative thereof.

26. The method of claim 21, wherein said hydrophobic coating comprises ethylcellulose.

27. The method of claim 25, wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

28. The method of claim 21, wherein said sustained release excipient comprises from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent.

29. The method of claim 21, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 24 hours.

30. The method of claim 21, further comprising compressing the mixture of said sustained release excipient and said tablet into tablets.

31. The method of claim 21, wherein said medicament comprises a therapeutically effective dose of albuterol or salts and derivatives of the same.

32. A method of treating a patient with albuterol comprising,

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of a albuterol, or a salt or derivative thereof, to said sustained release excipient, such that a final product is obtained having a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of albuterol for at least 12 hours.

adding an amount of albuterol effective to render a desired therapeutic effect;

tableting the resultant mixture such that a final product is obtained having a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol; and

administering said tablet to a patient at a predetermined dosage interval from about 12 to about 24 hours.

33. The method of claim 32, further comprising coating said tablets with a hydrophobic material to a weight gain from about 1% to about 20%.

34. The method of claim 32, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

35. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 89 to about 150 (ng-hours/ml).

36. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 57 to about 157 (ng-hours/ml).

37. The controlled release solid dossage form of claim 1 which, when orally administered to a fed patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 75 to about 162 (ng-hour s/ml).

38. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a mean peak plasma concentration ranging from about 7 to about 12 ng/ml.

39. The controlled release solid dossage form of claim 1 which, when orally administered to a fasting patient, provides a mean peak plasma concentration ranging from about 4.5 to about 19 ng/ml.

40. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a mean peak plasma concentration ranging from about 6 to about 16 ng/ml.

41. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a time to mean peak plasma concentration ranging from about 3 to about 10 hours.

42. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a time to mean peak plasma concentration ranging from about 3 to about 6 hours.

43. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a time to mean peak plasma concentration ranging from about 3 to about 8 hours.

44. The controlled release solid dosage form of claim 35 wherein the area under the plasma concentration curve, to infinity, ranges from about 112 to about 129 (ng-hours/ml).

45. The controlled release solid dosage form of claim 38 wherein the mean peak plasma concentration ranges from about, 9.5 to about 12 ng.

46. The controlled release solid dosage form of claim 42 wherein the time to mean peak plasma concentration ranges from about 3.5 to about 8 hours.

47. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein time to peak plasma concentration in a fasted patient divided by a time to peak plasma concentration in a fed patient ranges from about 0.50 to about 0.70.

48. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein peak plasma concentration in a fasted patient divided by peak plasma concentration in a fed patient ranges from about 0.90 to about 1.10.

* * * * *

EXHIBIT B

US005958456A

United States Patent [19]

Baichwal et al.

[11] Patent Number: 5,958,456

[45] Date of Patent: *Sep. 28, 1999

[54] **CONTROLLED RELEASE FORMULATION (ALBUTEROL)**

[75] Inventors: **Anand Baichwal**, Wappingers Falls, N.Y.; **Troy W. McCall**, New Milford, Conn.

[73] Assignee: **Edward Mendell Co., Inc.**, Patterson, N.Y.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **08/886,496**

[22] Filed: **Jul. 1, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/553,008, Nov. 3, 1995, Pat. No. 5,662,933, which is a continuation-in-part of application No. 08/118,924, Sep. 9, 1993, Pat. No. 5,455,046.

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/489**; 424/488; 424/457; 424/468

[58] **Field of Search** 424/489, 488, 424/457, 468

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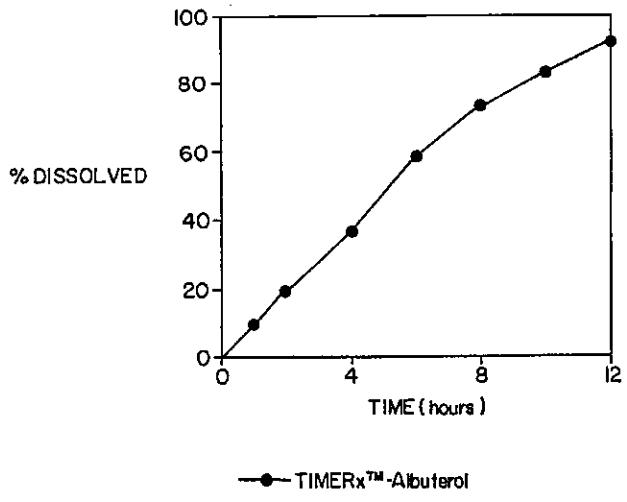
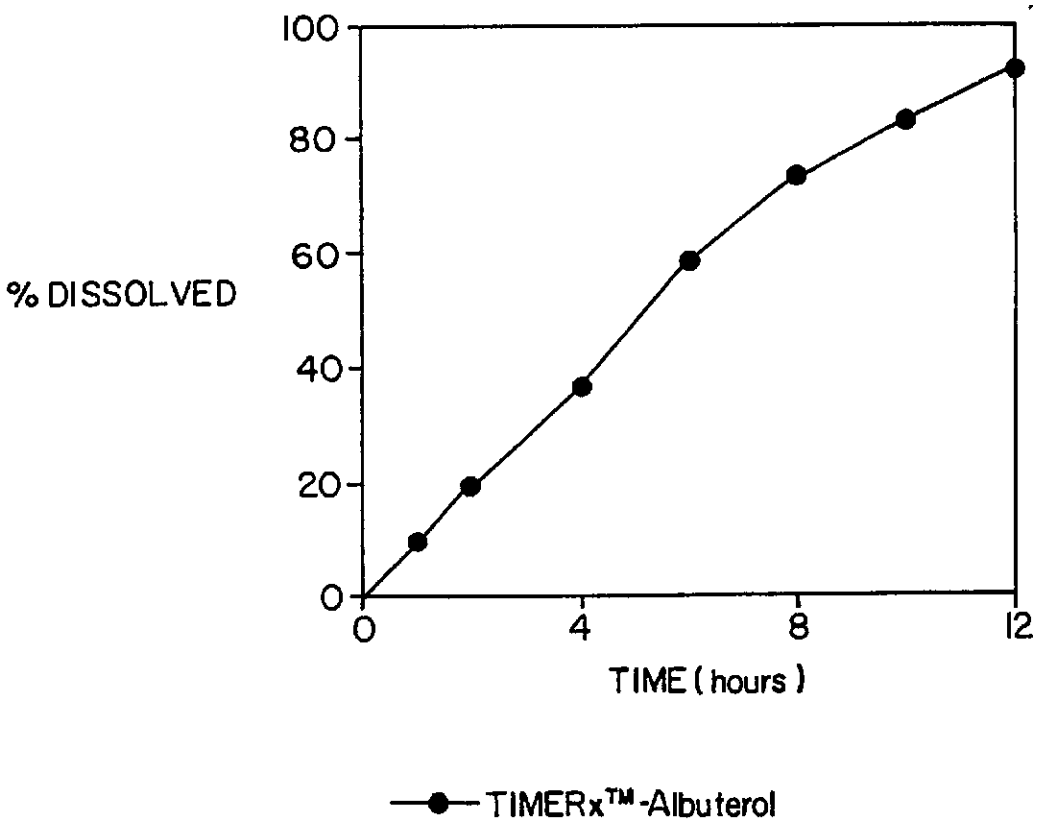
Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Davidson,Davidson & Kappel,LLC

[57] **ABSTRACT**

A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.

16 Claims, 3 Drawing Sheets

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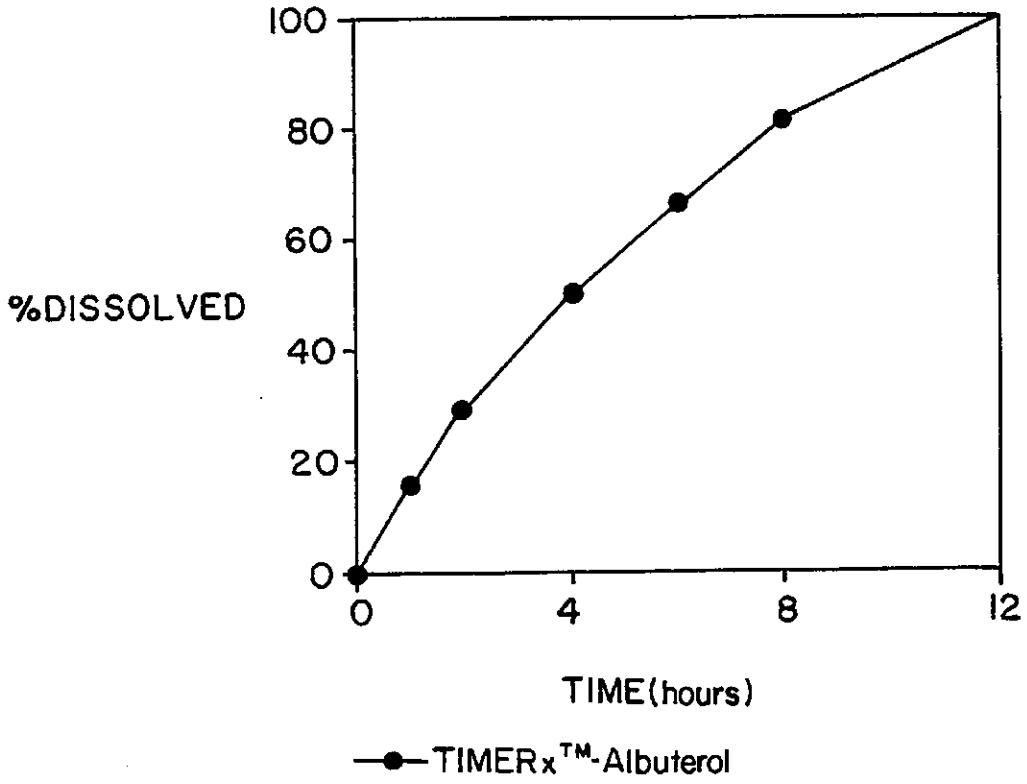
80
60
40
20
0
0
4
8
12
TIME (hours)
TIMERx™-Albuterol

FIG. 1


100
80
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40
20
0
%DISSOLVED
0
4
8
12
TIME(hours)
TIMERx™-Albuterol

FIG. 2

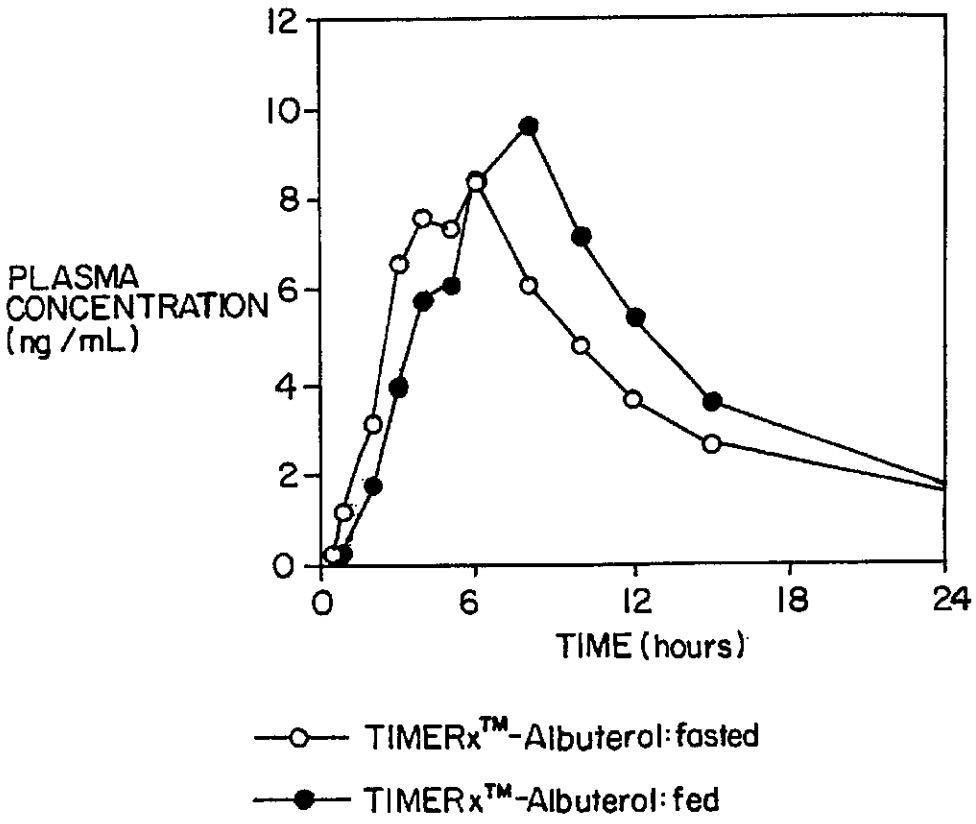
PLASMA CONCENTRATION (ng/mL)
12
10
8
6
4
2
0
0
6
12
18
24
TIME (hours)
TIMERx™-Albuterol: fasted
TIMERx™-Albuterol: fed

FIG. 3

CONTROLLED RELEASE FORMULATION (ALBUTEROL)

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 08/553,008, filed Nov. 3, 1995, now U.S. Pat. No. 5,662,933, which is a continuation-in-part of Ser. No. 08/118,924, filed Sep. 9, 1993, now U.S. Pat. No. 5,455,046.

FIELD OF THE INVENTION

The present invention relates to controlled release formulations which may be blended with a wide range of therapeutically active medicaments and made into controlled release solid dosage forms for oral administration.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number administrations. These advantages have been attained by a wide variety of methods. For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. In U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, hereby incorporated by reference in their entireties, it is reported that a controlled release excipient which is comprised of a synergistic combination of heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum, in an aqueous environment) is capable of being processed into oral solid dosage forms using either direct compression (i.e., dry granulation), following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the trade name TIMERx® from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-release pharmaceutical formulation containing xanthan gum wherein the xanthan gum comprises from about 7.5 to about 28 percent, by weight, of the formulation except for a formulation wherein the controlled release carrier comprises a mixture of 15–50 parts by weight dimethylsiloxane, 30–100 parts by weight silicic acid, 30–100 parts by weight mannans or galactans or a mixture thereof, 50–150 parts by weight xanthans and 5–75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of a controlled release formulation providing a novel and unexpected combination of suitable proportions of a homopolysaccharide such as, e.g., xanthan gum, a heteropolysaccharide, such as, e.g., locust bean gum, together with an inert diluent and a pharmacologically acceptable hydrophobic material, so as to provide an improvement in controlled release properties for such an active medicament.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release formulation for a therapeutically active medicament.

It is a further object of the present invention to provide a method for preparing a controlled release formulation for a therapeutically active medicament.

It is yet another object of the present invention to provide a controlled release excipient which may be used in the preparation of a sustained release oral solid dosage form of a therapeutically active medicament that provides an even rate of release of an active medicament.

It is a further object of the present invention to provide a controlled release excipient which, when combined with an effective amount of a bronchodilator, such as albuterol, is suitable for providing a sustained release of that medicament so as to provide a therapeutically effective blood level of the medicament for e.g., 12 or 24 hours, without allowing an excessive early release of medication, and where the release kinetics are unaffected by the contents of the patient's gastrointestinal tract.

It is yet a further object of the present invention to provide a method for treating patients with an active medication in controlled release form.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in-part to a controlled release formulation comprising a therapeutically effective amount of a medicament, and a controlled release excipient comprising a gelling agent and a swelling agent, such as, for example, a homopolysaccharide, a heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention, the ratio of the heteropolysaccharide gum to the homopolysaccharide gum is from about 1:3 to about 3:1. More preferably, the ratio is about 1:1. Preferably, the heteropolysaccharide gum includes xanthan gum and the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a sustained release oral solid dosage form for albuterol or salts or derivatives thereof in an amount necessary to render a therapeutic effect in a human patient. The albuterol is present in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical diluent so that the ratio of the inert diluent to the gelling agent is from about 1:8 to about 8:1. Preferably, the diluent is from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing. The diluent can also be a saccharide such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

The dosage form optionally includes a pharmaceutically acceptable hydrophobic material. Any pharmaceutically acceptable hydrophobic material may be suitably employed.

Suitable hydrophobic materials include carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing. Preferably, the hydrophobic material selected from cellulose ether, a cellulose ester and an alkylcellulose, such as ethylcellulose and carboxymethylcellulose. The hydrophobic material may be included in the dosage form in an amount effective to slow the hydration of the gelling agent when exposed to an environmental fluid.

The hydrophobic material is preferably present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form, and can also be present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

The medicament can be any medicament for which an orally administered controlled release form is desired. Preferably, the formulation is prepared to include a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

The controlled release solid dosage form can be prepared in any conventional orally administered dosage form, including a tablet, as a granular form and as a granular form administered in a gelatin capsule containing a sufficient amount of the granules to provide an effective dose of the included therapeutically active medicament. For a tablet dosage form, at least part of a surface of the tablet can optionally be coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight. Further, a granular dosage form can optionally be coated with a hydrophobic coating material to a weight gain that ranges from about 1% to about 20%. The hydrophobic material can be selected from, e.g., a cellulose ether, a cellulose ester and an alkylcellulose. The hydrophobic material can optionally be applied before, during or after the process of tableting. In addition, if there is a need for an early release of the active medicament, the coating can optionally be formulated to include from about 10 to about 40 percent of the total amount of the active medicament in a quick release external layer.

The invention also relates to methods for preparing a controlled release solid dosage form as described above for providing an active medicament in an amount effective for treating a patient for from 12 to about 24 hours. The method includes the steps of preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and optionally from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament to provide a final product having a ratio of medicament to gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC_∞"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC_∞ ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

In addition, for example, mean peak plasma concentrations (Cmax) ranging from about 7 to about 12 ng/ml or even from about, 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a Cmax ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

In another example, time to mean peak plasma concentration (Tmax) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a Tmax ranging from about 3 to about 6 hours (fasting patient) or from about 3 to about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC_∞ (fasting patient) to AUC_∞ (fed patient) that range from about 0.50 to about 0.70.

Further still, the formulation provides, for example ranges of Cmax (fasting patient) divided by Cmax (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a gelling agent of both hetero- and homo-polysaccharides which exhibit synergism, e.g., the combination of two or more polysaccharide gums produce a higher viscosity and faster hydration than that which would be expected by either of the gums alone, the resultant gel being faster-forming and more rigid.

In the present invention, it has been found that a sustained release excipient comprising only the gelling agent (heterodisperse polysaccharides, e.g., xanthan gum and locust bean gum, may not be sufficient to provide a suitable sustained release of an active medicament to provide a 12 or 24 hour formulation, when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid.

In certain embodiments, the present invention is related to the surprising discovery that by granulating the sustained release excipient with a solution or dispersion of a pharmacologically acceptable hydrophobic material prior to admixture of the sustained release excipient with the medicament and tableting, the medicament may provide therapeutically effective blood levels for extended periods of time, e.g., from about 12 to about 24 hours. The hydrophobic material is present in a range from about 0 to about 90%, by weight, of the sustained release excipient and in a preferred embodiment, is present in a range from about 1 to 20 percent of the sustained release excipient or from about 25 to about 75 percent of the sustained release excipient.

The sustained release excipient can be granulated with a pharmacologically acceptable hydrophobic material such as, for, example, an alkylcellulose, a cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropylcellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, a pre-manufactured direct compression diluent, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used. If the mixture is to be manufactured without a wet granulation step, and the final product is to be tableted, it is preferred that all or part of the inert

diluent comprise a pre-manufactured direct compression diluent. Such direct compression diluents are widely used in the pharmaceutical arts, and may be obtained from a wide variety of commercial sources. Examples of such pre-manufactured direct compression excipients include Emcocel® (microcrystalline cellulose, N.F.), Emdex® (dextrates, N.F.), and Tab-Fine® (a number of direct-compression sugars including sucrose, fructose, and dextrose), all of which are commercially available from Edward Mendell Co., Inc., Patterson, N.Y.). Other direct compression diluents include Anhydrous lactose (Lactose N.F., anhydrous direct tableting) from Sheffield Chemical, Union, N.J. 07083; Elcems® G-250 (Powdered cellulose, N.F.) from Degussa, D-600 Frankfurt (Main) Germany; Maltrin® (Agglomerated maltodextrin) from Grain Processing Corp., Muscatine, Iowa 52761; Neosorb 60® (Sorbitol, N.F., direct-compression) from Roquette Corp., 645 5th Ave., New York, N.Y. 10022; Nu-Tab® (Compressible sugar, N.F.) from Ingredient Technology, Inc., Pennsauken, N.J. 08110; Polyplasdone XL® (Crospovidone, N.F., cross-linked polyvinylpyrrolidone) from GAF Corp., New York, N.Y. 10020; Primojel® (Sodium starch glycolate, N.F., carboxymethyl starch) from Generichem Corp., Little Falls, N.J. 07424; Solka Floc® (Cellulose floc) from Edward Mendell Co., Carmel, N.Y. 10512; Fast-Flo Lactose® (Lactose N.F., spray dried) from Foremost Whey Products, Baraboo, Wis. 53913 and DMV Corp., Vehgel, Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized starch, N.F., compressible) from Colorcon, Inc., West Point, Pa. 19486. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75 percent gelling agent, and from about 30 to about 75 percent inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75 percent gelling agent and from about 15 to about 65 percent inert diluent.

The sustained release excipient of the present invention may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic material may be selected from an alkylcellulose such as ethylcellulose such as carboxymethyl-cellulose ("CMC"), other hydrophobic cellulosic materials, acrylic and/or methacrylic ester polymers, copolymers of acrylic and methacrylic esters, zein, waxes, other hydrophobic cellulosic materials, cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP"), hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid.

In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20 percent by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC), Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g, 1:20 or 1:40) of quaternary ammonium compounds).

Once the sustained release excipient of the present invention has been prepared, it is then possible to blend the same with the medicament, e.g., in a high shear mixer. In one embodiment, the formulation is prepared by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, optionally followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include drugs ranging in solubility from water soluble to water insoluble. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), antitussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In a preferred embodiment, the therapeutically active agents are sympathomimetics such as, dobutamine hydrochloride, dopamine hydrochloride, ephedrine sulfate, epinephrine, fenfluramine hydrochloride, isoetharine, isoproterenol, mephentermine sulfate, metaproterenol sulfate, metaraminol bitartrate, methoxamine hydrochloride, norepinephrine bitartrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, ritodrine hydrochloride, terbutaline sulfate, tetrahydrozoline hydrochloride, triprolidine and pseudoephedrine, xylometazoline hydrochloride, isoproterenol and dobutamine as well as beta2 selective adrenergic agonists, including, for example, terbutaline, albuterol, isoetharine, pirbuterol and bitolterol (GOODMAN AND GILMAN's, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Eighth Edition, the disclosure of which is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274

by the National Academy of Sciences, pages 63–258, incorporated herein in its entirety, may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857–884, hereby incorporated by reference in its entirety), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the inventive formulation can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following addition of drug and lubricant powder, or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In dry granulation techniques, the excipients, i.e., the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed with an active medicament and the mixture is then formed into tablets and the like by compression, without the addition of water or other solvent.

In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The sustained release excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. When the final product to be manufactured is tablets, the complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000–1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active (drug) is high, a pharmaceutical formulator may choose to wet granulate the active medicament with other excipients to attain a more compact tablet. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 300 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg.

The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an

average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic material, such as, e.g., a hydrophobic polymer, to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic material included in the tablet coating may be the same or different material as compared to the hydrophobic material which is optionally granulated with the sustained release excipient.

In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead or the hydrophobic coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100–555.

In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10 μ if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2-selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

Preparation

The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or capsules. Whatever the formulation, it is preferred that such

pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

Dissolution Testing

The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

Bioavailability Study

A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC0-t, AUC0-∞, mean peak plasma concentration ("Cmax") and $time_{\Delta}$ to mean peak plasma concentration ("Tmax") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

EXAMPLES 1–2

Preparation of Controlled Release Formulations with Carboxymethylcellulose and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1–2 are set forth in Table 1 below:

TABLE 1

The hydrophobic polymer is carboxymethylcellulose ("CMC").

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt (mg)	334.6	204.7
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	2.6

The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

EXAMPLES 3–4

Preparation of Controlled Release Formulations with Cellulose Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra,

but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

	Component	Example 3	Example 4
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	CAP	10	30
4.	Dextrose	60	40
5.	Water	10*	17*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

TABLE 5

	Component	Example 3	Examples 4
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

TABLE 6

	Example 3	Example 4
Time (hrs)		
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.8	5.8

The tablet tested in Example 4 provided the most prolonged release in the dissolution test.

EXAMPLES 5–6

Preparation of Controlled Release Formulations with Polyvinyl Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

TABLE 7

	Component	Example 5	Example 6
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	PVAP	10	30
4.	Dextrose	60	40
5.	Water	18*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

TABLE 8

	Component	Example 5	Example 6
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

TABLE 9

	Example 5	Example 6
Time (hrs)		
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.9	8.6

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

EXAMPLES 7–8

Preparation of Controlled Release Formulations with Hydroxypropylmethylcellulose Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean

gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

TABLE 10

	Component	Example 7	Example 8
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	HPMCP	10	30
4.	Dextrose	60	40
5.	Water	13*	18*

*Removed during processing.

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

TABLE 11

	Component	Example 7	Example 8
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

TABLE 12

	Example 7	Example 8
Time (hrs)		
0 (% release)	0.0	0.0
1	33.7	32.7
2	48.2	42.8
4	63.9	60.3
6	74.8	71.2
8	79.6	74.6
10	85.6	82.3
12	87.0	87.2
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

EXAMPLES 9–12

Preparation of Controlled Release Formulations with Ethylcellulose Coating and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1–2, supra, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9–12 are detailed by Table 13, below.

TABLE 13

	Component	Excipient for Examples 9–12
1.	Xanthan gum	12%
2.	Locust bean gum	18
3.	Dextrose	65
4.	EAD*	5*

*EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease ®, from Colorcon.

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) was mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets were coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°–50° C.; charge per batch 1 kg; dry air—Conair Prostyle 1250, 60°–70° C.). The tablets were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The proportions of the tablets are set forth in Table 14 below:

TABLE 14

	Component	Percent
1.	SRE*	8.2%
2.	Albuterol sulfate	5.3
3.	Polyvinyl acetate phthalate	5.0
4.	Sodium stearyl fumarate	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 15, below. The columns are identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex. 11) and 4% (Ex. 12) coating by weight.

TABLE 15

Time (hrs)	Ex. 9 Uncoated	Ex. 10 2%	Ex. 11 3%	Ex. 12 4% (coat % w/w)
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5
Tablet wt (mg)	181.4			
Diameter (in)	⅜			
Hardness (Kp)	7.9			

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9–12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH—time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16

Fed/Fast Dissolution Protocol

	"Fasted"	"Fed"
Apparatus:	Type III	Type III
Media:	0–1 hr pH 1.5 1–2 hr pH 3.5 2–4 hr pH 5.5 4–12 hr pH 7.5	30% peanut oil
Agitation:	15 cpm	15 cpm
Volume:	250 mL	250 mL

TABLE 17

Fed/Fast Dissolution Results

Time (hrs)	"Fasted" Uncoated	"Fasted" 2%	"Fed" Uncoated	"Fed" 2%
0 (% release)	0.0	0.0	0.0	0.0
1	48.8	15.5	28.8	18.4
2	68.5	28.8	49.8	39.9
4	87.2	49.5	91.9	78.9
6	96.1	65.9	100.0	97.3
8	100.0	80.7	100.0	100.0
12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

Results and Discussion

FIGS. 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in FIG. 3. FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of FIG. 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 though 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max}, T_{max}, and AUC_{28} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

TABLE 18

Albuterol Pharmacokinetics

Parameter	TIMERx fasted	TIMERx fed
Cmax		
mean	10.5	10.6
% CV	39.0	31.0
Tmax		
mean	4.5	7.0
% CV	29.0	23.0
AUCInf		
mean	113.4	128.1
% CV	30.0	20.0

Ratios	Cmax	Tmax	AUC Inf
TIMERx fasted:TIMERx fed	0.98	0.64	0.89
TIMERx fed:TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

TABLE 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC_{∞}	57.3–156.2	75.6–161.1
Cmax	4.6–18.4	6.0–15.9
Tmax	3.0–6.0	3.0–8.0

Parameter	TIMERx-fed
AUC_{∞}	89.9–149.2
Cmax	7.0–11.9
Tmax	3.0–10.0

Conclusion

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various

modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

a sustained release excipient comprising a gelling agent; a pharmaceutically acceptable hydrophobic material; and an inert pharmaceutical diluent wherein the ratio of said inert diluent to said gelling agent is from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid.

2. The controlled release solid dosage form according to claim 1 wherein said inert diluent is selected from the group consisting of pharmaceutically acceptable saccharides, polyhydric alcohols, pre-manufactured direct compression diluents, and mixtures of any of the foregoing.

3. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

4. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

5. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25 percent to about 50 percent, by weight, of the solid dosage form.

6. The controlled release solid dosage form according to claim 1, wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

7. The controlled release solid dosage form according to claim 1 which is a tablet.

8. The controlled release solid dosage form according to claim 1, which is in granulate form.

9. The controlled release solid dosage form according to claim 8, wherein said granulate is coated with a hydrophobic material to a weight gain from about 1 percent to about 20 percent.

10. The controlled release solid dosage form according to claim 1, wherein the medicament comprises an amount of albuterol equivalent to about 4 mg to about 16 mg of albuterol free base.

11. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising

preparing of a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent, from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to about 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding a therapeutically effective amount of a medicament to said excipient, such that

a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

12. The method of claim 11, further comprising compressing said mixture of said sustained release excipient and said medicament into tablets.

13. The method of claim 11, wherein said medicament is albuterol or a salt or derivative thereof.

14. The method of claim 13, further comprising coating the resultant tablets with a hydrophobic coating to a weight gain from about 1 percent to about 20 percent.

15. A method of treating a patient with albuterol comprising:

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of albuterol or a salt or derivative thereof to said sustained release excipient, tableting the resultant mixture into tablets such that said tablets have a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol for at least 12 hours; and

administering said tablet to a patient on a once-a-day or twice-a-day basis.

16. The method of claim 15, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

* * * * *

EXHIBIT C

US007276250B2

(12) **United States Patent**
Baichwal et al.

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(45) **Date of Patent: Oct. 2, 2007**

(54) **SUSTAINED RELEASE FORMULATIONS OF OXYMORPHONE**

(75) Inventors: **Anand R. Baichwal**, Wappingers Falls, NY (US); **Huai-Hung Kao**, Syosset, NY (US); **Troy W. McCall**, Germantown, TN (US)

(73) Assignee: **Penwest Pharmaceuticals Company**, Danbury, CT (US)

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(58) **Field of Classification Search** 424/468, 424/474, 490, 475, 476, 477, 479, 480, 482, 424/491, 494, 495, 497, 498
See application file for complete search history.

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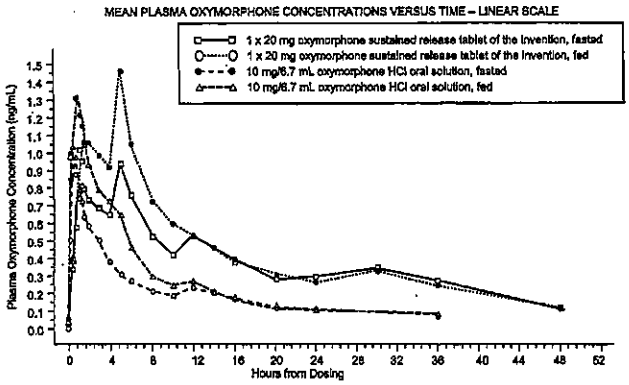
Primary Examiner—Lakshmi S. Channavajjala
(74) *Attorney, Agent, or Firm*—Wilmer Cutler Pickering Hale & Dorr, LLP

(57) **ABSTRACT**

Sustained release formulations of oxymorphone or pharmaceutically acceptable salts thereof; methods for making the sustained release formulations of oxymorphone or pharmaceutically acceptable salts thereof; and methods for using the sustained release formulations of oxymorphone or pharmaceutically acceptable salts thereof to treat patients suffering from pain are provided.

16 Claims, 1 Drawing Sheet



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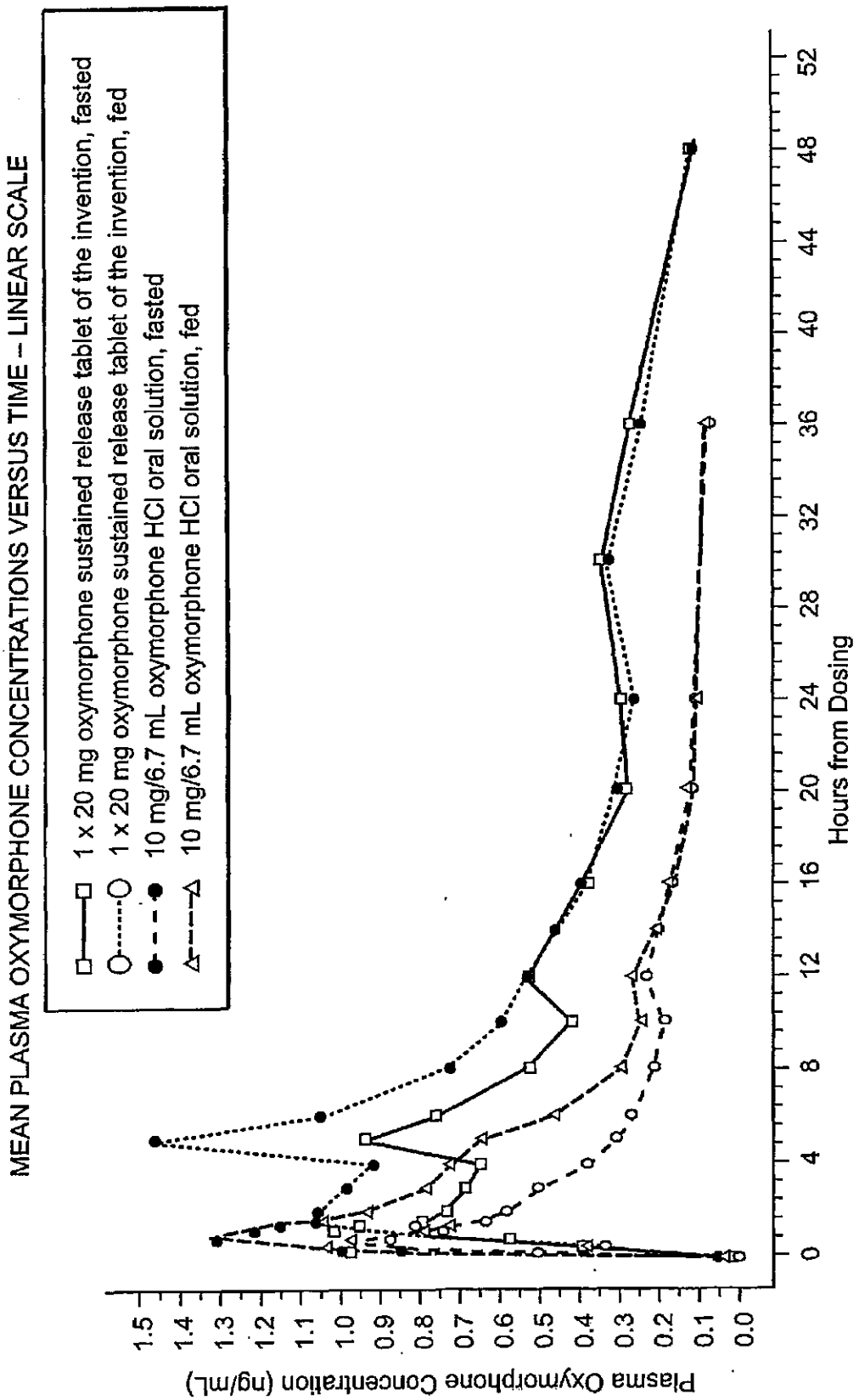
MEAN PLASMA OXYMORPHONE CONCENTRATIONS VERSUS TIME – LINEAR SCALE
1 x 20 mg oxymorphone sustained release tablet of the invention, fasted
1 x 20 mg oxymorphone sustained release tablet of the invention, fed
10 mg/6.7 mL oxymorphone HCl oral solution, fasted
10 mg/6.7 mL oxymorphone HCl oral solution, fed
Plasma Oxymorphone Concentration (ng/mL)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
Hours from Dosing
0
4
8
12
16
20
24
28
32
36
40
44
48
52

SUSTAINED RELEASE FORMULATIONS OF OXYMORPHONE

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/329,426 filed Oct. 15, 2001, U.S. Provisional Application No. 60/329,352 filed Oct. 15, 2001, and to U.S. Provisional Application No. 60/303,357 filed Jul. 6, 2001, the disclosures of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The invention provides sustained release formulations of oxymorphone and pharmaceutically acceptable salts thereof; methods for making the sustained release formulations of oxymorphone and pharmaceutically acceptable salts thereof; and methods for using the sustained release formulations of oxymorphone and pharmaceutically acceptable salts thereof to treat patients suffering from pain.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the United States suffer from severe pain that is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely used for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, a 10 mg oral immediate release tablet formation of oxymorphone HCl was marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6 alpha and beta hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. Scheduled rather than "as needed" administration of opioids is currently recommended in guidelines for their use in treating chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate 4-hourly administrations in order to maintain optimal levels of analgesia in patients with chronic pain. Moreover, immediate release oxymorphone exhibits low oral bioavailability, because oxymorphone is extensively metabolized in the liver.

There is a need in the art for new formulations of oxymorphone that require less frequent dosing. The invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The invention provides compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, where the sustained release delivery system comprises at least one hydrophilic compound, at least one cross-linking agent (which may be cationic) and at least one pharmaceutical diluent. The sustained release delivery system may further comprise one or more additional hydrophobic polymers or cross-linking compounds. The compositions may optionally comprise an outer coating comprising at least one water insoluble compound, and optionally one or more plasticizers and/or water soluble compounds.

The invention provides compositions comprising an inner core and an outer sustained release coating, where the inner core comprises oxymorphone or a pharmaceutically acceptable salt thereof and the outer sustained release coating comprises at least one water insoluble compound. The outer sustained release coating may optionally further comprise one or more plasticizers and/or water soluble compounds.

The invention provides methods for treating pain in patients by administering an effective amount of any of the compositions of the invention. The pain may be moderate to severe, and may be acute or chronic.

The invention also provides methods for making such compositions.

These and other aspects of the invention are described in detail herein.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 is a linear scale graph, without standard deviations, showing the mean oxymorphone plasma concentration versus time for patients treated with the sustained release oxymorphone tablets of the invention after fasting (A), for patients treated with sustained release oxymorphone tablets of the invention after a high fat meal (B), for patients treated with an oxymorphone solution after fasting (C), and for patients treated with an oxymorphone solution after a high fat meal (D).

DETAILED DESCRIPTION OF THE INVENTION

To overcome the difficulties associated with the very low bioavailability of the oral immediate release formulation of oxymorphone and with a 4 hourly dosing frequency of oxymorphone, the invention provides an oral sustained release formulation of oxymorphone comprising an analgesically effective amount of oxymorphone or a pharmaceutically acceptable salt thereof. The bioavailability of the oral sustained release formulations of the invention is sufficiently high that the sustained release formulations can be used to treat patients suffering from pain with only once or twice daily dosing.

The invention provides compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, wherein the sustained release delivery system comprises (i) at least one hydrophilic compound, at least one cross-linking agent, and at least one pharmaceutical diluent; (ii) at least one hydrophilic compound, at least one cross-linking agent, at least one pharmaceutical diluent, and at least one hydrophobic polymer; (iii) at least one hydrophilic compound, at least one cross-linking agent, at least one pharmaceutical diluent, and at least one cationic cross-linking agent different from the

first cross-linking agent; (iv) at least one hydrophilic compound, at least one cross-linking agent, at least one pharmaceutical diluent, at least one cationic cross-linking compound different from the first cross-linking agent, and at least one hydrophobic polymer; (v) at least one hydrophilic compound, at least one cationic cross-linking compound, and at least one pharmaceutical diluent; or (vi) at least one hydrophilic compound, at least one cationic cross-linking compound, at least one pharmaceutical diluent, and at least one hydrophobic compound.

The oxymorphone may be homogeneously dispersed in the sustained release delivery system. Preferably, the oxymorphone or pharmaceutically acceptable salt thereof may be present in the composition in an amount of about 1 mg to about 200 mg, more preferably in an amount of about 1 mg to about 100 mg, even more preferably in an amount of about 5 mg to about 80 mg. Preferably, the sustained release delivery system may be present in the composition in an amount from about 80 mg to about 420 mg, more preferably from about 80 mg to about 360 mg, even more preferably from about 80 mg to about 200 mg. "Oxymorphone" includes oxymorphone, metabolites thereof, derivatives thereof, and/or pharmaceutically acceptable salts thereof. Metabolites of oxymorphone include, for example, 6-hydroxy-oxymorphone (e.g., 6-α-hydroxy-oxymorphone and/or 6-β-hydroxy-oxymorphone).

Oxymorphone may be in the form of any pharmaceutically acceptable salt known in the art. Exemplary pharmaceutically acceptable salts include hydrochloric, sulfuric, nitric, phosphoric, hydrobromic, maleric, malic, ascorbic, citric, tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, napthalinesulfonic, linoleic, linolenic acid, and the like. The hydrochloride salt of oxymorphone is preferred.

The sustained release delivery system comprises at least one hydrophilic compound. The hydrophilic compound preferably forms a gel matrix that releases the oxymorphone or the pharmaceutically acceptable salt thereof at a sustained rate upon exposure to liquids. The rate of release of the oxymorphone or the pharmaceutically acceptable salt thereof from the gel matrix depends on the drug's partition coefficient between the components of the gel matrix and the aqueous phase within the gastrointestinal tract. In the compositions of the invention, the weight ratio of oxymorphone to hydrophilic compound is generally in the range of about 1:0.5 to about 1:25, preferably in the range of about 1:0.5 to about 1:20. The sustained release delivery system generally comprises the hydrophilic compound in an amount of about 20% to about 80% by weight, preferably in an amount of about 20% to about 60% by weight, more preferably in an amount of about 40% to about 60% by weight, still more preferably in an amount of about 50% by weight.

The hydrophilic compound may be any known in the art. Exemplary hydrophilic compounds include gums, cellulose ethers, acrylic resins, polyvinyl pyrrolidone, protein-derived compounds, and mixtures thereof. Exemplary gums include heteropolysaccharide gums and homopolysaccharide gums, such as xanthan, tragacanth, pectins, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean gums, and gellan gums. Exemplary cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses. Preferred cellulose ethers include hydroxyethyl celluloses, hydroxypropyl celluloses, hydroxypropylmethyl-celluloses, carboxy methylcelluloses, and mixtures thereof. Exemplary acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. In some embodiments, the hydrophilic compound is preferably a gum, more preferably a heteropolysaccharide gum, most preferably a xanthan gum or derivative thereof. Derivatives of xanthan gum include, for example, deacylated xanthan gum, the carboxymethyl esters of xanthan gum, and the propylene glycol esters of xanthan gum.

In another embodiment, the sustained release delivery system may further comprise at least one cross-linking agent. The cross-linking agent is preferably a compound that is capable of cross-linking the hydrophilic compound to form a gel matrix in the presence of liquids. As used herein, "liquids" includes, for example, gastrointestinal fluids and aqueous solutions, such as those used for in vitro dissolution testing. The sustained release delivery system generally comprises the cross-linking agent in an amount of about 0.5% to about 80% by weight, preferably in an amount of about 2% to about 54% by weight, more preferably in an amount of about 20% to about 30% by weight more, still more preferably in an amount of about 25% by weight.

Exemplary cross-linking agents include homopolysaccharides. Exemplary homopolysaccharides include galactomannan gums, such as guar gum, hydroxypropyl guar gum, and locust bean gum. In some embodiments, the cross-linking agent is preferably a locust bean gum or a guar gum. In other embodiments, the cross-linking agents may be alginic acid derivatives or hydrocolloids.

When the sustained release delivery system comprises at least one hydrophilic compound and at least one cross-linking agent, the ratio of hydrophilic compound to cross-linking agent may be from about 1:9 to about 9:1, preferably from about 1:3 to about 3:1.

The sustained release delivery system of the invention may comprise one or more cationic cross-linking compounds. Cationic cross-linking compound may be used instead of or in addition to the cross-linking agent. The cationic cross-linking compounds may be used in an amount sufficient to cross-link the hydrophilic compound to form a gel matrix in the presence of liquids. The cationic cross-linking compound is present in the sustained release delivery system in an amount of about 0.5% to about 30% by weight, preferably from about 5% to about 20% by weight.

Exemplary cationic cross-linking compounds include monovalent metal cations, multivalent metal cations, and inorganic salts, including alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, and mixtures thereof. For example, the cationic cross-linking compound may be one or more of calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, or mixtures thereof.

When the sustained release delivery system comprises at least one hydrophilic compound and at least one cationic cross-linking compound, the ratio of hydrophilic compound to cationic cross-linking compound may be from about 1:9 to about 9:1, preferably from about 1:3 to about 3:1.

Two properties of desirable components of this system (e.g., the at least one hydrophilic compound and the at least one cross-linking agent; or the at least one hydrophilic compound and at least one cationic cross-linking compound) that form a gel matrix upon exposure to liquids are fast hydration of the compounds/agents and the ability to form a gel matrix having a high gel strength. These two properties, which are needed to achieve a slow release gel matrix, are maximized in the invention by the particular combination of compounds (e.g., the at least one hydrophilic compound and

the at least one cross-linking agent; or the at least one hydrophilic compound and the at least one cationic cross-linking compound). For example, hydrophilic compounds (e.g., xanthan gum) have excellent water-wicking properties which provide fast hydration. The combination of hydrophilic compounds with materials that are capable of cross-linking the rigid helical ordered structure of the hydrophilic compound (e.g., cross-linking agents and/or cationic cross-linking compounds) thereby act synergistically to provide a higher than expected viscosity (i.e., high gel strength) of the gel matrix.

The sustained release delivery system further comprises one or more pharmaceutical diluents known in the art. Exemplary pharmaceutical diluents include monosaccharides, disaccharides, polyhydric alcohols and mixtures thereof. Preferred pharmaceutical diluents include, for example, starch, lactose, dextrose, sucrose, microcrystalline cellulose, sorbitol, xylitol, fructose, and mixtures thereof. In other embodiments, the pharmaceutical diluent is water-soluble, such as lactose, dextrose, sucrose, or mixtures thereof. The ratio of pharmaceutical diluent to hydrophilic compound is generally from about 1:8 to about 8:1, preferably from about 1:3 to about 3:1. The sustained release delivery system generally comprises one or more pharmaceutical diluents in an amount of about 20% to about 80% by weight, preferably about 35% by weight. In other embodiments, the sustained release delivery system comprises one or more pharmaceutical diluents in an amount of about 40% to about 80% by weight.

The sustained release delivery system of the invention may comprise one or more hydrophobic polymers. The hydrophobic polymers may be used in an amount sufficient to slow the hydration of the hydrophilic compound without disrupting it. For example, the hydrophobic polymer may be present in the sustained release delivery system in an amount of about 0.5% to about 20% by weight, preferably in an amount of about 2% to about 10% by weight, more preferably in an amount of about 3% to about 7% by weight, still more preferably in an amount of about 5% by weight.

Exemplary hydrophobic polymers include alkyl celluloses (e.g., C_{1-6} alkyl celluloses, carboxymethylcellulose), other hydrophobic cellulosic materials or compounds (e.g., cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate), polyvinyl acetate polymers (e.g., polyvinyl acetate phthalate), polymers or copolymers derived from acrylic and/or methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and mixtures thereof. The hydrophobic polymer is preferably methyl cellulose, ethyl cellulose or propyl cellulose, more preferably ethyl cellulose.

The compositions of the invention may be further admixed with one or more wetting agents (such as polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil, polyethoxylated fatty acid from hydrogenated castor oil) one or more lubricants (such as magnesium stearate, sodium stearyl fumarate, and the like), one or more buffering agents, one or more colorants, and/or other conventional ingredients.

In other embodiments, the invention provides oral sustained release solid dosage formulations comprising from about 1 mg to 200 mg oxymorphone hydrochloride, preferably from about 5 mg to about 80 mg oxymorphone hydrochloride; and about 80 mg to about 200 mg of a sustained release delivery system, preferably from about 120 mg to about 200 mg of a sustained release delivery system, more preferably about 160 mg of a sustained release delivery system; where the sustained release delivery system comprises about 8.3 to about 41.7% locust bean gum, preferably about 25% locust bean gum; about 8.3 to about 41.7% xanthan gum, preferably about 25% xanthan gum; about 20 to about 55% dextrose, preferably about 35% dextrose; about 5 to about 20% calcium sulfate dihydrate, preferably about 10% calcium sulfate dihydrate; and about 2 to 10% ethyl cellulose, preferably about 5% ethyl cellulose.

In other embodiments, the invention provides oral sustained release solid dosage formulations comprising from about 1 mg to 200 mg oxymorphone hydrochloride, preferably from about 5 mg to about 80 mg oxymorphone hydrochloride; and about 200 mg to about 420 mg of a sustained release delivery system, preferably from about 300 mg to about 420 mg of a sustained release delivery system, more preferably about 360 mg of a sustained release delivery system; where the sustained release delivery system comprises about 8.3 to about 41.7% locust bean gum, preferably about 25% locust bean gum; about 8.3 to about 41.7% xanthan gum, preferably about 25% xanthan gum; about 20 to about 55% dextrose, preferably about 35% dextrose; about 5 to about 20% calcium sulfate dihydrate, preferably about 10% calcium sulfate dihydrate; and about 2 to 10% ethyl cellulose, preferably about 5% ethyl cellulose.

The sustained release formulations of oxymorphone are preferably orally administrable solid dosage formulations which may be, for example, tablets, capsules comprising a plurality of granules, sublingual tablets, powders, or granules; preferably tablets. The tablets may be an enteric coating or a hydrophilic coating.

The sustained release delivery system in the compositions of the invention may be prepared by dry granulation or wet granulation, before the oxymorphone or pharmaceutically acceptable salt thereof is added, although the components may be held together by an agglomeration technique to produce an acceptable product. In the wet granulation technique, the components (e.g., hydrophilic compounds, cross-linking agents, pharmaceutical diluents, cationic cross-linking compounds, hydrophobic polymers, etc.) are mixed together and then moistened with one or more liquids (e.g., water, propylene glycol, glycerol, alcohol) to produce a moistened mass which is subsequently dried. The dried mass is then milled with conventional equipment into granules of the sustained release delivery system. Thereafter, the sustained release delivery system is mixed in the desired amounts with the oxymorphone or the pharmaceutically acceptable salt thereof and, optionally, one or more wetting agents, one or more lubricants, one or more buffering agents, one or more coloring agents, or other conventional ingredients, to produce a granulated composition. The sustained release delivery system and the oxymorphone may be blended with, for example, a high shear mixer. The oxymorphone is preferably finely and homogeneously dispersed in the sustained release delivery system. The granulated composition, in an amount sufficient to make a uniform batch of tablets, is subjected to tableting in a conventional production scale tableting machine at normal compression pressures, i.e., about 2,000-16,000 psi. The mixture should not be compressed to a point where there is subsequent difficulty with hydration upon exposure to liquids.

The average particle size of the granulated composition is from about 50 μm to about 400 μm, preferably from about 185 μm to about 265 μm. The average density of the granulated composition is from about 0.3 g/ml to about 0.8 g/ml, preferably from about 0.5 g/ml to about 0.7 g/ml. The tablets formed from the granulations are generally from about 6 to about 8 kg hardness. The average flow of the granulations are from about 25 to about 40 g/sec.

In other embodiments, the invention provides sustained release coatings over an inner core comprising oxymorphone or a pharmaceutically acceptable salt thereof. For example, the inner core comprising oxymorphone or a pharmaceutically acceptable salt thereof may be coated with a sustained release film which, upon exposure to liquids, releases the oxymorphone or the pharmaceutically acceptable salt thereof from the core at a sustained rate.

In one embodiment, the sustained release coating comprises at least one water insoluble compound. The water insoluble compound is preferably a hydrophobic polymer. The hydrophobic polymer may be the same as or different from the hydrophobic polymer used in the sustained release delivery system. Exemplary hydrophobic polymers include alkyl celluloses (e.g., C_{1-6} alkyl celluloses, carboxymethylcellulose), other hydrophobic cellulosic materials or compounds (e.g., cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate), polyvinyl acetate polymers (e.g., polyvinyl acetate phthalate), polymers or copolymers derived from acrylic and/or methacrylic acid esters, zein, waxes (alone or in admixture with fatty alcohols), shellac, hydrogenated vegetable oils, and mixtures thereof. The hydrophobic polymer is preferably, methyl cellulose, ethyl cellulose or propyl cellulose, more preferably ethyl cellulose. The sustained release formulations of the invention may be coated with a water insoluble compound to a weight gain from about 1 to about 20% by weight.

The sustained release coating may further comprise at least one plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, polyethylene glycol, or mixtures thereof.

The sustained release coating may also contain at least one water soluble compound, such as polyvinylpyrrolidones, hydroxypropylmethylcelluloses, or mixtures thereof. The sustained release coating may comprise at least one water soluble compound in an amount from about 1% to about 6% by weight, preferably in an amount of about 3% by weight.

The sustained release coating may be applied to the oxymorphone core by spraying an aqueous dispersion of the water insoluble compound onto the oxymorphone core. The oxymorphone core may be a granulated composition made, for example, by dry or wet granulation of mixed powders of oxymorphone and at least one binding agent; by coating an inert bead with oxymorphone and at least one binding agent; or by spheronizing mixed powders of oxymorphone and at least one spheronizing agent. Exemplary binding agents include hydroxypropylmethylcelluloses. Exemplary spheronizing agents include microcrystalline celluloses. The inner core may be a tablet made by compressing the granules or by compressing a powder comprising oxymorphone or the pharmaceutically acceptable salt thereof.

In other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with a sustained release coating, as described herein. In still other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with a hydrophobic polymer, as described herein. In still other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with an enteric coating, such as cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimelliate, or mixtures thereof. In still other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with a hydrophobic polymer, as described herein, and further coated with an enteric coating, as described herein. In any of the embodiments described herein, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, may optionally be coated with a hydrophilic coating which may be applied above or beneath the sustained release film, above or beneath the hydrophobic coating, and/or above or beneath the enteric coating. Preferred hydrophilic coatings comprise hydroxypropylmethylcellulose.

The invention provides methods for treating pain by administering an effective amount of the sustained release formulations of oxymorphone to a patient in need thereof. An effective amount is an amount sufficient to eliminate all pain or to alleviate the pain (i.e., reduce the pain compared to the pain present prior to administration of the oxymorphone sustained release formulation). "Sustained release" means that the oxymorphone or pharmaceutically acceptable salt thereof is released from the formulation at a controlled rate so that therapeutically beneficial blood levels (but below toxic levels) of the oxymorphone or pharmaceutically acceptable salt thereof are maintained over an extended period of time. The sustained release formulations of oxymorphone are administered in an amount sufficient to alleviate pain for an extended period of time, preferably about 8 hours to about 24 hours, more preferably for a period of about 12 hours to about 24 hours. The oxymorphone sustained release oral solid dosage formulations of the invention may be administered one to four times a day, preferably once or twice daily, more preferably once daily. The pain may be minor to moderate to severe, and is preferably moderate to severe. The pain may be acute or chronic. The pain may be associated with, for example, cancer, autoimmune diseases, infections, surgical traumas, accidental traumas or osteoarthritis. The patient may be an animal, preferably a mammal, more preferably a human.

In certain embodiments, upon oral ingestion of the oxymorphone sustained release formulation and contact of the formulation with gastrointestinal fluids, the sustained release formulation swells and gels to form a hydrophilic gel matrix from which the oxymorphone is released. The swelling of the gel matrix causes a reduction in the bulk density of the formulation and provides the buoyancy necessary to allow the gel matrix to float on the stomach contents to provide a slow delivery of the oxymorphone. The hydrophilic matrix, the size of which is dependent upon the size of the original formulation, can swell considerably and become obstructed near the opening of the pylorus. Since the oxymorphone is dispersed throughout the formulation (and consequently throughout the gel matrix), a constant amount of oxymorphone can be released per unit time in vivo by dispersion or erosion of the outer portions of the hydrophilic gel matrix. The process continues, with the gel matrix remaining bouyant in the stomach, until substantially all of the oxymorphone is released.

In certain embodiments, the chemistry of certain of the components of the formulation, such as the hydrophilic compound (e.g., xanthan gum), is such that the components are considered to be self-buffering agents which are substantially insensitive to the solubility of the oxymorphone and the pH changes along the length of the gastrointestinal tract. Moreover, the chemistry of the components is believed to be similar to certain known muco-adhesive substances,

such as polycarbophil. Muco-adhesive properties are desirable for buccal delivery systems. Thus, the sustained release formulation can loosely interact with the mucin in the gastrointestinal tract and thereby provide another mode by which a constant rate of delivery of the oxymorphone is achieved.

The two phenomenon discussed above (buoyancy and muco-adhesive properties) are mechanisms by which the sustained release formulations of the invention can interact with the mucin and fluids of the gastrointestinal tract and provide a constant rate of delivery of the oxymorphone.

When measured by USP Procedure Drug Release USP 23 (incorporated by reference herein in its entirety), the sustained release formulations of the invention exhibit an in vitro dissolution rate of about 15% to about 50% by weight oxymorphone after 1 hour, about 45% to about 80% by weight oxymorphone after 4 hours, and at least about 80% by weight oxymorphone after 10 hours. The in vitro and in vivo release characteristics of the sustained release formulations of the invention may be modified using mixtures of one or more different water insoluble and/or water soluble compounds, using different plasticizers, varying the thickness of the sustained release film, including providing release-modifying compounds in the coating, and/or by providing passageways through the coating.

When administered orally to patients the sustained release formulations of the invention exhibit the following in vivo characteristics: (a) a peak plasma level of oxymorphone occurs within about 2 to about 6 hours after administration; (b) the duration of the oxymorphone analgesic effect is about 8 to about 24 hours; and (c) the relative oxymorphone bioavailability is about 0.5 to about 1.5 compared to an orally administered aqueous solution of oxymorphone.

While the compositions of the invention may be administered as the sole active pharmaceutical compound in the methods described herein, they can also be used in combination with one or more compounds which are known to be therapeutically effective against pain.

The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the compositions of the invention. The kits may further comprise other pharmaceutical compounds known in the art to be therapeutically effective against pain, and instructions for use.

EXAMPLES

The following examples are for purposes of illustration only and are not intended to limit the scope of the appended claims.

Examples 1 and 2

Two sustained release delivery systems were prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry was prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry was added to the dry blended mixture, and granulated for another 3 minutes. The granulation was then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation was then milled using 20 mesh screen. The relative quantities of the ingredients are listed in Table 1.

TABLE 1

Sustained Release Delivery System Excipient	Example 1 %	Example 2 %
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)[1]	(10)[1]	(20.0)[1]
Total	100.0	100.0

[1]Volatile, removed during processing

Examples 3 to 7

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the sustained release delivery system of Example 1. The quantities of ingredients per tablet are listed in Table 2.

TABLE 2

Component	Ex. 3 mg	Ex. 4 mg	Ex. 5 mg	Ex. 6 mg	Ex. 7 mg
Oxymorphone HCl, USP	5	10	20	40	80
Sustained release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
OPADRY ® (colored)	7.48	7.68	8.08	8.88	10.48
OPADRY ® (clear)	0.94	0.96	1.01	1.11	1.31

Examples 8 and 9

Two batches of tablets were prepared as described above for Examples 1-7, using the sustained release delivery system of Example 1. One batch was formulated to provide relatively fast sustained release, the other batch was formulated to provide relatively slow sustained release. Compositions of the tablets are shown in Table 3.

TABLE 3

Ingredients	Example 8 slow release mg/tablet	Example 9 fast release mg/tablet
Oxymorphone HCl, USP	20	20
Sustained Release Delivery System	360	160
Silicified Microcrystalline Cellulose, NF	20	20
Sodium stearyl fumarate, NF	4	2
Coating (color)	12.12	12.12
Total weight	416.12	214.12

The tables of Examples 8 and 9 were tested for in vitro release rate according to USP Procedure Drug Release USP 23. The results are shown in Table 4.

TABLE 4

Time (hr)	Example 8 slow release	Example 9 fast release
0.5	18.8%	21.3%
1	27.8%	32.3%

TABLE 4-continued

Time (hr)	Example 8 slow release	Example 9 fast release
2	40.5%	47.4%
3	50.2%	58.5%
4	58.1%	66.9%
5	64.7%	73.5%
6	70.2%	78.6%
8	79.0%	86.0%
10	85.3%	90.6%
12	89.8%	93.4%

Example 10

Clinical Study

A clinical study was conducted to (1) assess the relative bioavailability (rate and extent of absorption) of oxymorphone sustained release (20 mg) (fast release formulation of Example 9) compared to oral solution oxymorphone (10 mg) under fasted conditions, (2) to assess the relative bioavailability of oxymorphone sustained release (20 mg) compared to oral solution oxymorphone (10 mg) under fed conditions, (3) to assess the relative bioavailability of oxymorphone sustained release (20 mg) fed compared to oxymorphone sustained release (20 mg) fasted, (4) to assess the relative bioavailability of oral solution oxymorphone fed compared to oral solution oxymorphone fasted, and (5) to assess the relative safety and tolerability of sustained release oxymorphone (20 mg) under fed and fasted conditions.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment A and Treatment C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment B and Treatment D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment A and Treatment B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment C and Treatment D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments A and B were of oxymorphone sustained release 20 mg tablets. Subjects randomized to Treatment A received a single oral dose of one 20 mg oxymorphone sustained release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment B received a single oral dose of one 20 mg oxymorphone sustained release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments C and D were of oxymorphone HCl solutions, USP, 1.5 mg/ml injection 10 ml vials. Subjects randomized to Treatment C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment D received a single oral dose of 10 mg (6.7 mil) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds). The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

The subjects were screened within 14 days prior to study enrollment. The screening procedure included medical history, physical examination (height, weight, frame size, vital signs, and ECG), and clinical laboratory tests (hematology, serum chemistry, urinalysis, HIV antibody screen, Hepatitis B surface antigen screen, Hepatitis C antibody screen, and a screen for cannabinoids).

During the study, the subjects were to remain in an upright position (sitting or standing) for 4 hours after the study drug was administered. Water was restricted 2 hours predose to 2 hours postdose. During the study, the subjects were not allowed to engage in any strenuous activity.

Subjects reported to the clinic on the evening prior to each dosing. The subjects then observed a 10-hour overnight fast. On Day 1, subjects randomized to Treatment B and Treatment D received a high-fat breakfast within 30 minutes prior to dosing. A standardized meal schedule was then initiated with lunch 4 hours postdose, dinner 10 hours postdose, and a snack 13 hours postdose. On Day 2, a standardized meal was initiated with breakfast at 0815, lunch at 1200, and dinner at 1800. Subjects randomized to Treatment A and Treatment B received a snack at 2100 on Day 2.

Vital signs (sitting for 5 minutes and consisting of blood pressure, pulse, respiration, and temperature), and 12-lead ECG were assessed at the—13 hour point of each check-in period and at the completion of each period. A clinical laboratory evaluation (hematology, serum chemistry, urinalysis) and a brief physical examination were performed at the—13 hour of each check-in period and at the completion of the each period. Subjects were instructed to inform the study physician and/or nurses of any adverse events that occurred during the study.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment A and Treatment B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment C and Treatment D. A total of 80 blood samples (560 ml) per subject were drawn during the study for drug analysis. Plasma samples were separated by centrifugation, and then frozen at −70° C., and kept frozen until assayed.

An LC/MS/MS method was developed and validated for the determination of oxymorphone in human EDTA plasma. Samples were spiked with internal standard, d_3-oxymorphone, and placed on the RapidTrace® (Zymark Corporation, Hopkinton, Mass.) for automatic solid phase extraction. Extracts were dried under nitrogen and reconstituted with acetonitrile before injection onto an LC/MS/MS. The Perkin Elmer Sciex API III+, or equivalent, using a turbo ion spray interface was employed in this study. Positive ions were monitored in the MRM mode.

The pharmacokinetic parameters shown in Table 5 were computed from the plasma oxymorphone concentration-time data.

TABLE 5

AUC(0-t)	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.
AUC(0-inf)	Area under the drug concentration-time curve from time zero to infinity. AUC(0-inf) = AUC(0-t) + Ct/Kel, where Kel is the terminal elimination rate constant.
AUC(0-24)	Partial area under the drug concentration-time curve from time zero to 24 hours.
Cmax	Maximum observed drug concentration.
Tmax	Time of the observed maximum drug concentration.
Kel	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.
T1/2el	Half life, the time required for the concentration to decline by 50%, calculated as LN(2)/Kel

Terminal elimination rate constants were computed using linear regression of a minimum of three time points, at least two of which were consecutive. Kel values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus, T1/2el, AUC(0-inf), C1/F, MRT, and LN-transformed T1/2el, AUC(0-inf), and C1/F were also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding Tmax and Frel), and the LN-transformed parameters C_{max}, AUC (0-24), AUC(0-t), AUC(0-inf), C1/F, and T1/2el. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square). The following treatment comparisons of relative rate and extent of absorption were made: Treatment B versus Treatment A, Treatment A versus Treatment C (dose normalized to 20 mg). Treatment B versus Treatment D (dose normalized to 20 mg), and Treatment D versus Treatment C (dose normalized to 20 mg for both treatments). The 90% confidence intervals of the ratios of the treatment least squares parameter means were calculated. Tmax was analyzed using the Wilcoxon Signed Ranks test. Summary statistics were presented for Frel.

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

A total of 26 analytical runs were required to process the clinical samples from this study. Of these 26 analytical runs, 26 were acceptable for oxymorphone. Standard curves for the 26 analytical runs in EDTA plasma used in this study covered a range of 0.0500 to 20.000 mg/ml with a limit of quantitation of 0.0500 ng/ml for both compounds. Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 14.23% for oxymorphone.

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

The mean oxymorphone plasma concentration versus time curves for Treatments A, B, C, and D are presented in FIG. 1 (linear scale, without standard deviation).

Individual concentration versus time curves were characterized by multiple peaks which occurred in the initial 12-hour period following the dose. In addition, a small "bump" in plasma oxymorphone concentration was generally observed in the 24 to 48 hour post-dose period.

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment B versus Treatment A are summarized in Table 6.

TABLE 6

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments B and A

	Plasma Oxymorphone					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	1.7895	0.6531	1.1410	0.4537	125.4-191.0	158.2
Tmax(hr)	5.65	9.39	5.57	7.14		
Auc(0-24)(ng * hr/ml)	14.27	4.976	11.64	3.869	110.7-134.0	122.3
AUC(O-t)(ng * hr/ml)	19.89	6.408	17.71	8.471	100.2-123.6	111.9
AUC(O-inf) (ng * hr/ml)	21.29	6.559	19.29	5.028	105.3-133.9	119.6
T 1/2el(hr)	12.0	3.64	12.3	3.99	57.4-155.2	106.3

Treatment B = 1 × 20 mg oxymorphone sustained release Tablet, Fed: test
Treatment A = 1 × 20 mg oxymorphone sustained release Tablet, Fasted: reference

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment A versus Treatment C are summarized in Table 7.

TABLE 7

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment A		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	1.1410	0.4537	2.2635	1.0008	33.4-66.0	49.7
Tmax(hr)	5.57	7.14	0.978	1.14		
Auc(0-24)(ng * hr/ml)	11.64	3.869	12.39	4.116	82.8-104.6	93.7
AUC(0-l)(ng * hr/ml	17.71	8.471	14.53	4.909	107.7-136.3	122.0
AUC(0-inf) (ng * hr/ml)	19.29	5.028	18.70	6.618	80.2-108.4	94.3
T 1/2el(hr)	12.3	3.99	16.2	11.4	32.9-102.1	67.5

Treatment A = 1 × 20 mg oxymorphone sustained release Tablet, Fasted: test
Treatment C = 10 mg/6.7 ml oxymorphone HCl Oral Solution, Fasted: Dose Normalized to 20 ng: reference.

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment D versus Treatment C are summarized in Table 8.

TABLE 8

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment B		Treatment D			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	1.7895	0.6531	3.2733	1.3169	42.7-65.0	50.0
Tmax(hr)	5.65	9.39	1.11	0.768		
Auc(0-24)(ng * hr/ml)	14.27	4.976	17.30	5.259	74.4-90.1	82.2
AUC(0-t)(ng * hr/ml)	19.89	6.408	19.28	6.030	92.5-114.1	103.3
AUC(0-inf) (ng * hr/ml)	21.29	6.559	25.86	10.03	75.0-95.2	85.1
T 1/2el(hr)	12.0	3.64	20.6	19.3	31.9-86.1	59.0

Treatment B = 1 × 20 mg oxymorphone sustained release Tablet, Fed: test
Treatment D = 10 mg/6.7 ml oxymorphone HCl Oral Solution, Fed: Dose Normalized to 20 mg: reference.

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment D versus Treatment C are summarized in Table 9.

TABLE 9

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment D		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	3.2733	1.3169	2.2635	1.0008	129.7-162.3	146.0
Tmax(hr)	1.11	0.768	0.978	1.14		
Auc(0-24)(ng * hr/ml)	17.30	5.259	12.39	4.116	128.5-150.3	139.4

TABLE 9-continued

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment D		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-t)(ng * hr/ml)	19.20	6.030	14.53	4.909	117.9-146.5	132.2
AUC(0-inf) (ng * hr/ml)	25.86	10.03	18.70	6.618	118.6-146.6	132.6
T 1/2el(hr)	20.6	19.3	16.2	11.4	87.3-155.9	121.6

Treatment D = 10 mg/6.7 ml oxymorphone HCl Oral Solution, Fed: Dose Normalized to 20 mg: test.
Treatment C = 10 mg/6.7 ml oxymorphone HCl Oral Solution, Fasted: Dose Normalized to 20 mg: reference.

The relative bioavailability calculations are summarized in Table 10.

TABLE 10

Mean (S.D.) Relative Oxymorphone Bioavailability Determined from AUC (0-inf) and AUC (0-24)

	Frel BA		Frel AC		Frel BD		Frel DC	
AUC(0-inf)	1.169	(0.2041)	1.040	(0.1874)	0.8863	(0.2569)	1.368	(0.4328)
AUC(0-24)	1.299	(0.4638)	(0.9598)	(0.2151)	0.8344	(0.100)	1.470	(0.3922)

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone sustained release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the sustained release formulation and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone Cmax, but less of an effect on oxymorphone AUC from oxymorphone sustained release tablets. Least Squares (LS) mean Cmax was 58% higher and LS mean AUC(0-t) and AUC(0-inf) were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from AUC (0-inf) since mean Frel was 1.17. Individual Frel values based on AUC (0-24) were similar (less than 20% different) to Frel values based on AUC (0-inf) for all but 2 subjects. Comparison of mean Frel from AUC (0-inf) to mean Frel from AUC (0-24) is misleading, because not all subjects had a value for AUC (0-inf). Mean Tmax values were similar (approximately 5.6 hours), and no significant different in Tmax was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean Cmax was 50% higher and LS mean AUC(0-t) and AUC(0-inf) were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from AUC(0-inf) since mean Frel was 1.37. Individual Frel values based on AUC(0-24) were similar (less than 20% different) to Frel values based on AUC(0-inf.) for all but 5 subjects. Comparison of mean Frel from AUC(0-inf) to mean Frel from AUC(0-24) is misleading because not all subjects had a value for AUC(0-inf). Mean Tmax (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone sustained release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean AUC(0-t) was 17% higher for oxymorphone sustained release, whereas LS mean AUC(0-inf) values were nearly equal (mean ratio=99%). However, AUC(0-t) is not the best parameter to evaluate bioavailability since the plasma concentrations were measured for 48 hours for the sustained release formulation versus 36 hours for the oral solution. Mean Frel values calculated from AUC(0-inf) and AUC(0-24), (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

There were differences in parameters reflecting rate of absorption. LS mean Cmax was 49% lower for oxymorphone sustained release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the sustained release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone sustained release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean AUC(0-inf) was 12% lower for oxymorphone sustained release. Mean Frel values calculated from AUC(0-inf) and AUC(0-24), (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. There were differences in parameters reflecting rate of absorption. LS mean Cmax was 46% lower

for oxymorphone sustained release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean Tmax was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the sustained release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability following administration of oxymorphone sustained release tablets. LS mean ratios were 97% for AUC(0-t) and 91% for Cmax (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from AUC(0-24), since mean Frel was 0.97. AUC(0-inf) was not a reliable measure for bioavailability since half-life could not be estimated accurately, and in many cases at all. Half-life estimates were not accurate because in the majority of subjects, the values for half-life were nearly as long or longer (up to 2.8 times longer) as the sampling period. Mean Tmax was later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone sustained release 20 mg tablets exhibited similar availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for AUC (0-t) was 104.5%. Mean Frel (0.83) calculated from AUC(0-24) also showed similar extent of oxymorphone availability between the two treatments. There were differences in parameters reflecting rate of absorption. LS mean Cmax was 57% lower for oxymorphone sustained release tablets compared to the dose-normalized oral solution. Mean Tmax was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the sustained release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability from oxymorphone sustained release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean AUC(0-t) was 14% higher for oxymorphone sustained release. Mean Frel (0.87) calculated from AUC (0-24) also indicated similar extent of availability between the treatments. There were differences in parameters reflecting rate of absorption. LS mean Cmax was 40% lower for oxymorphone sustained release tablets compared to the dose-normalized oral solution. Mean Tmax was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the sustained release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone sustained release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment, based on LN-transformed data. Tmax was unaffected by food; however, LS mean Cmax was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean Cmax and AUC values were increased approximately 50 and 30%, respectively. Tmax was unaffected by food. Under both fed and fasted conditions, oxymorphone sustained release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment.

Bioavailability following oxymorphone sustained release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean Cmax and AUC values for each treatment. Tmax was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, Cmax was decreased 35% in the presence of food. Tmax was unaffected by food. Under both fed and fasted conditions, oxymorphone sustained release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

Various modifications of the invention, in addition to those described herein, will be apparent to one skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim **1**, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim **1**, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulate sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

5. The oral sustained release formulation of claim **1**, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims **1-5**.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim **7**, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim **7**, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim **7**, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim 7, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 7-11.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 1-5.

14. The solid dosage formulation of claim 13, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of anyone of claims 7-11.

16. The solid dosage formulation of claim 15, wherein the solid dosage formulation is a tablet.

* * * * *

EXHIBIT D

Press Release

IMPAX Comments on Status of ANDA for Generic Opana(R) ER

HAYWARD, Calif., Oct 04, 2007 (BUSINESS WIRE) -- IMPAX Laboratories, Inc. (OTC:IPXL) today confirmed reports that it has provided notice to Endo Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. that it has submitted an Abbreviated New Drug Application (ANDA) for oxymorphone hydrochloride extended-release tablets CII, generic of Opana (R) ER, to the U.S. Food and Drug Administration (FDA). IMPAX's ANDA, as amended, contains a Paragraph IV certification stating that the Company believes its product does not infringe US Patent No. 7,276,250, or that the patent is invalid or unenforceable. Following an acceptance for filing by the FDA the Company was informed by the agency that it has rescinded its initial acceptance. IMPAX believes that the rescission is inappropriate and is working with the FDA to correct any deficiencies of the ANDA.

Endo Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. manufacture and market Opana ER for the treatment of moderate to severe pain. According to Wolters Kluwer Health, U.S. sales of Opana ER tablets were approximately $42.9 million in the 12 months ended August 31, 2007.

About IMPAX Laboratories, Inc.

IMPAX Laboratories, Inc. is a technology based specialty pharmaceutical company applying its formulation expertise and drug delivery technology to the development of controlled-release and specialty generics in addition to the development of branded products. IMPAX markets its generic products through its Global Pharmaceuticals division and markets its branded products through the IMPAX Pharmaceuticals division. Additionally, where strategically appropriate, IMPAX has developed marketing partnerships to fully leverage its technology platform. IMPAX Laboratories is headquartered in Hayward, California, and has a full range of capabilities in its Hayward and Philadelphia facilities. For more information, please visit the Company's Web site at: www.impaxlabs.com.

"Safe Harbor" statement under the Private Securities Litigation Reform Act of 1995:

To the extent any statements made in this news release contain information that is not historical, these statements are forward-looking in nature and express the beliefs and expectations of management. Such statements are based on current expectations and involve a number of known and unknown risks and uncertainties that could cause IMPAX's future results, performance or achievements to differ significantly from the results, performance or achievements expressed or implied by such forward-looking statements. Such risks and uncertainties include, but are not limited to, possible adverse effects resulting from the delisting of and suspension of trading in IMPAX's stock, the SEC proceeding to determine whether to suspend or revoke the registration of IMPAX's securities under section 12 of the Securities Exchange Act, IMPAX's delay in filing its 2004 Form 10-K, its Form 10-Q for each of the first three quarters of 2005 and 2006, its Form 10-K for 2005 and 2006, and its Form 10-Q for the first quarter of 2007, the actual time that will be required to complete the filing of IMPAX's delinquent periodic reports, IMPAX's ability to obtain sufficient capital to fund its operations, the difficulty of predicting FDA filings and approvals, consumer acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, IMPAX's ability to successfully develop and commercialize pharmaceutical products, IMPAX's reliance on key strategic alliances, the uncertainty of patent litigation, the availability of raw materials, the regulatory environment, dependence on patent and other protection for innovative products, exposure to product liability claims, fluctuations in operating results and other risks detailed from time to time in IMPAX's filings with the Securities and Exchange Commission. Forward-looking statements speak only as to the date on which they are made, and IMPAX undertakes no obligation to update publicly or revise any forward-looking statement, regardless of whether new information becomes available, future developments occur or otherwise.

SOURCE: IMPAX Laboratories, Inc.

Company Contacts:
IMPAX Laboratories, Inc.
Larry Hsu, Ph.D. President & CEO
510-476-2000, Ext. 1111

Arthur A. Koch, Jr. CFO
215-933-0351
www.impaxlabs.com
or
Investor Relations Contacts:
Lippert/Heilshorn & Associates, Inc.
Kim Sutton Golodetz, 212-838-3777
kgolodetz@lhai.com
Bruce Voss, 310-691-7100
bvoss@lhai.com
www.lhai.com

JS 44 (Rev. 11/04)

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I. (a) PLAINTIFFS
Endo Pharmaceuticals Inc. and
Penwest Pharmaceuticals Co.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Jack B. Blumenfeld/Julia Heaney,
MORRIS, NICHOLS, ARSHT & TUNNELL LLP, 1201 North Market Street,
P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200

DEFENDANTS
Impax Laboratories, Inc.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing (**Do not cite jurisdictional statutes unless diversity**):
28 U.S.C. § 2201 and 35 U.S.C. § 100 et seq.
Brief description of cause:
declaratory judgment and patent infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 **DEMAND $** CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE _____ DOCKET NUMBER _____

DATE November 15, 2007

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

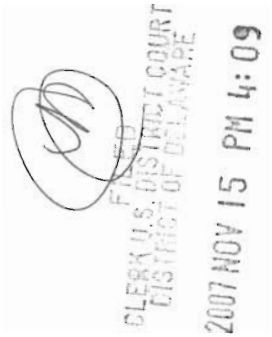
Date and Attorney Signature. Date and sign the civil cover sheet.

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

07-731

Civil Action No. _____



ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 3 COPIES OF AO FORM 85.

NOV 15 2007

(Date forms issued)

(Signature of Party or their Representative)

ZACHARY MICHAEL BORL

(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action